MIND: A Prospective, Multicenter Study of Artemis, a **M**inimally **I**nvasive **N**euro Evacuation **D**evice, in the Removal of Intracerebral Hemorrhage

Protocol
CLP 11899.B

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Device Name
Artemis Neuro Evacuation Device

Sponsor
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CLP 11899.B Protocol Synopsis	
Study Title:	**MIND: A Prospective, Multicenter Study of Artemis, a Minimally Invasive Neuro Evacuation Device, in the Removal of Intracerebral Hemorrhage**
Study Objective:	The primary objective of this multicenter randomized controlled study is to compare the safety and efficacy of minimally invasive hematoma evacuation with the Artemis Neuro Evacuation Device to best medical management for the treatment of intracerebral hemorrhage (ICH).
Study Design:	This study will be a prospective, randomized, multi-center study that will enroll up to 500 patients at up to 50 sites globally.
Indication:	US/Canada: The Artemis Neuro Evacuation Device is used for the controlled aspiration of tissue and/or fluid during surgery of the Ventricular System or Cerebrum in conjunction with a Penumbra Aspiration Pump. The Penumbra Aspiration Pump is indicated as a vacuum source for the Penumbra Aspiration Systems. EU/ROW: The Artemis Neuro Evacuation Device is used for the controlled aspiration of tissue and/or fluid during surgery of the Ventricular System or Cerebrum for patients age 18 or older in conjunction with a Penumbra Aspiration Pump. The Penumbra Aspiration Pump is indicated as a vacuum source for the Penumbra Aspiration Systems.
Patient Population:	Patients with moderate-large volume supratentorial ICH who present within 24 hours of symptom onset.
Study Device:	Artemis Neuro Evacuation Device
Study Duration:	It is anticipated enrollment will take approximately 4 years. Subjects will be in the study for approximately one year from enrollment to last follow-up.
Follow-up:	Subjects will undergo follow-up at 24 or 72 hours, 7 days, 30 days, 90 days, 180 days, and 365 days.
Inclusion Criteria:	1. Patient age ≥ 18 and ≤ 80 2. Supratentorial ICH of volume ≥ 20 and ≤ 80 cc (measured using A x B x C/2 method) 3. Hemostasis as confirmed by no arterial spot sign (may perform additional scan(s) every 6 hours to demonstrate hemostasis) 4. NIHSS ≥ 6 5. GCS ≥ 5 and ≤ 15 6. Historical mRS 0 or 1 7. Symptom onset < 24 hours prior to initial CT/MR 8. MIS must be initiated within 72 hours of ictus/bleed

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	9. SBP must be < 180 mmHg and controlled at this level for at least 6 hours
Exclusion Criteria:	1. Imaging a. "Arterial Spot Sign" identified on final CTA indicating expanding hemorrhage b. Hemorrhagic lesion such as a vascular malformation (cavernous malformation, AVM etc.), aneurysm, and/or neoplasm c. Hemorrhagic conversion of an underlying ischemic stroke d. Infratentorial hemorrhage e. Primary thalamic ICH (where the center of the hemorrhage emulates from the thalamus) f. Associated intra-ventricular hemorrhage requiring treatment for IVH-related mass effect or shift due to trapped ventricle (EVD for ICP management is allowed) g. Midbrain extension/involvement h. Absolute contraindication to CTA, conventional angiography, and MRA 2. Coagulation Issues a. Absolute requirement for long-term anti-coagulation (e.g., mechanical valve replacement (bio-prostatic valve is permitted), high risk atrial fibrillation) b. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency c. Platelet count < 100 x 10^3 cells/mm^3 or known platelet dysfunction d. INR > 1.4, elevated prothrombin time or activated partial thromboplastin time (aPTT), which cannot be corrected or otherwise accounted for (i.e., lupus anti-coagulant) e. Use of direct factor Xa inhibitors (e.g. apixaban, rivaroxaban, fondaparinux) within last 48 hours 3. Patient Factors a. Traumatic ICH b. High risk atrial fibrillation (e.g., mitral stenosis with atrial fibrillation) and/or symptomatic carotid stenosis c. Requirement for emergent surgical decompression or uncontrolled ICP after EVD d. Unable to obtain consent per Institution Review Board/Ethics Committee policy e. Pregnancy or positive pregnancy test (either serum or urine). Women of child-bearing potential must have a negative pregnancy test prior to enrollment f. Severe active infection requiring treatment (e.g. sepsis or purulent wound) at the time of enrollment g. Renal failure indicated by creatinine > 2 mg/dL or undergoing dialysis

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	h. Any comorbid disease or condition expected to compromise survival or ability to complete follow-up assessments through 365 days i. Based on investigator's judgement, patient is unwilling or unable to comply with protocol follow up appointment schedule j. Active drug or alcohol use or dependence that, in the opinion of the site investigator would interfere with adherence to study requirements k. Currently participating in another interventional (drug, device, etc.) clinical trial. Patients in observational, natural history, and/or epidemiological studies not involving intervention are eligible
Randomization	Subjects will be randomized to either minimally invasive hematoma evacuation with the Artemis Neuro Evacuation Device with medical management (MIS group) or best medical management alone (2:1) (MM group). After a subject is randomized to a study arm they will be considered enrolled. Randomization will be balanced based upon presenting condition (Hemphill Score) and hemorrhage location (primarily lobar vs. primarily deep).
Primary Endpoints:	• Efficacy Endpoint: 180 day global disability assessed via the ordinal modified Rankin score (mRS) • Safety Endpoint: Rate of mortality at 30 days
Secondary Efficacy Endpoints:	• Weighted mRS at 180 days • mRS of ≤ 3 at 180 days • mRS of ≤ 2 at 180 days • mRS at 365 days • Stroke Impact Scale – Mobility at 180 days • Stroke Impact Scale – ADLs at 180 days • Stroke Impact Scale – Mobility at 365 days • Stroke Impact Scale – ADLs at 365 days • EQ-5D-5L at 180 days • EQ-5D-5L at 365 days • Length of hospital stay • Length of ICU stay • Length of procedure
Primary Statistical Hypothesis	The null hypothesis is that the cumulative odds ratio for mRS at 180 days in the MIS group compared to MM group is less than or equal to 1. The alternative hypothesis is that the cumulative odds ratio for mRS at 180 days is greater than 1.
Primary Statistical Test	The final analysis is a logistic regression analysis of the ordinal 180 day mRS scores with scores of 5 and 6 treated as a single category. The primary efficacy

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	endpoint is met if the overall treatment effect is positive at a one-sided alpha of 0.02.
Sample Size	Based on simulations, a sample size of 500 has 81% power for a cumulative odds ratio of 1.7 with a one-sided alpha of 0.025. The minimum sample size is 200 patients (133 MIS and 67 MM).

1. Introduction and Rationale

Intracerebral hemorrhage (ICH) is the most common subtype of hemorrhagic stroke, accounting for 10 – 15% of all strokes and affecting between 10 and 30 people per 100,000.[1-3] The incidence of ICH is increasing, likely secondary to the increasing mean age of the population.[4,5]

ICH is a devastating disease with the poorest prognosis of all stroke subtypes.[6] The estimated mortality rate is 40% at 1 month, 50% at 1 year and more than 70% at 5 years.[3,7,8] The majority of survivors are dependent at follow-up.[9] If there is a concomitant component of intraventricular hemorrhage and hydrocephalus, outcomes are even worse.[10-13]

Due to the high intensity and the long duration of care required for patients, ICH is ranked amongst the most costly of all neurological diagnoses.[14] Russell et al. reported that the average cost for patients experiencing mortality from their initial hemorrhage was greater than 16,500 US dollars (patients admitted between 1999 and 2002). These costs were much greater in survivors, increasing to more than 28,000 for the initial hospitalization, with an additional 16,000 incurred during the first year after discharge.[14]{Russell, 2006 #3026} A recent RCT of an Australian population provides additional forecasts for long-term associated costs, with an annual estimate between 3 to 5 years at approximately $5,807, increasing to $7,607 at 10 years, and an overall lifetime cost of $54,956.[15]

Despite extensive study, benefits from medical or surgical intervention are not well established and have not been consistently demonstrated to reduce mortality or improve outcomes in patients with ICH. This is further compounded by the lack of evidence from efforts of neuroprotection.[16]{Lyden, 2007 #1604} This lack of progress is reflected by the mortality rate of ICH, which has been relatively stable for the past several decades.[3,17]

Medical management consists of admission to an intensive care unit (ICU) or monitored stroke unit, airway assessment and management, control of hypertension, and assessment for, and reversal/correction of, any inherent or pharmacologically induced coagulopathy. The presence of hydrocephalus or elevated intracranial pressures, secondary to mass effect or concomitant intraventricular hemorrhage (IVH), may require emergent placement of a ventricular drainage catheter. More pronounced mass effect or herniation may require a craniectomy/craniotomy for emergent evacuation of the hemorrhage and/or decompression.[18,19]

Multiple randomized controlled trials of more aggressive medical management strategies as well as conventional surgical evacuation have failed to demonstrate an improvement in clinical outcomes or survival.[13,18,20-25]

1.1 Randomized Trials of Medical Management of Intracranial Hemorrhage

In the FAST Trial, 841 patients with ICH were randomized to receive placebo or one of two doses, 20 μg or 80 μg per kilogram of bodyweight, of recombinant factor VIIa (rFVIIa) within 4 hours of symptom onset. Although the higher dose of

rFVIIa was associated with a significantly lower rate of hematoma expansion, this effect did not translate to an improvement in clinical outcomes or mortality.[26] Moreover, the increased incidence of thrombotic complications in the rFVIIa group did not account for the failure of the trial to demonstrate a clinical benefit.

Similarly, two pilot trials of aggressive medical management of blood pressure, INTERACT and ATACH, did not demonstrate any benefit for survival or favorable clinical outcome when compared to more conservative medical management.[20,27] INTERACT did show a reduction in hematoma growth with aggressive BP management.[20] A larger trial of aggressive blood pressure control, INTERACT II, failed to demonstrate a reduced rate of death or major disability with aggressive management, but did show a modest, but statistically significant, improvement in the ordinal analysis of modified Rankin scores (mRS) for the intensive management group.[28]

Trials of aggressive management of cerebral edema with mannitol have also failed.[21,22,24]

1.2 Randomized Trials of Conventional Open Surgical Management of Intracranial Hemorrhage

Two large randomized controlled trials of conventional open surgery for intracranial hemorrhage (Surgical Trial in Intracerebral Hemorrhage (STICH I and STICH II) have both demonstrated no beneficial effect from hematoma evacuation.[13,23] In STICH I, early surgical management was compared to standard medical management in a series of 1033 patients with supratentorial ICH. Three-quarters of subjects in both arms of STICH I demonstrated poor clinical outcomes or died. Subgroup analyses of the STICH I cohort indicated a potential benefit for those subjects with superficial ICH (within 1 cm of the cortical surface) without intra-ventricular extension. On the basis of this observation, the STICH II trial was designed specifically to assess the effects of conventional surgical management in this group of subjects. In STICH II, 601 patients with superficial hemorrhages were randomized between early surgery and conservative management with 59% of subjects in the surgical group and 61% of the subjects in the medical management groups had unfavorable outcomes. A trend toward improved mortality at 6 months (18% in the early surgery group and 24% in the medical management group) failed to reach significance ($p = 0.095$).

Taken together, this data provides strong evidence that the conventional open surgical management of intracerebral hemorrhage is not beneficial in patients with ICH who are not in need of emergent, life-saving decompression.

1.3 Rationale for Study

ICH is thought to induce neurological injury in a biphasic manner.[29] The primary neurological injury is caused by the direct mechanical destruction of neurons by the original bleed.[2] This form of injury is not treatable per se, with the exception

perhaps of medical interventions designed to reduce or eliminate hematoma early expansion from re-bleeding. As discussed above, several medical interventions have been demonstrated to successfully limit hematoma growth, but none have been associated with a compelling clinical benefit.

Secondary injury to the brain surrounding the hematoma has been theorized to be the sequelae of locally increased pressure resulting in reduced regional perfusion as well as a direct cytotoxic effect of blood breakdown products on adjacent brain tissue (hemotoxicity). [29] It is believed that this secondary injury is manifested as peri-hematomal edema (PHE) on imaging studies.[30-33]

In patients with ICH undergoing serial CT studies over the course of several weeks, Zazulia et al. observed the progression of mass effect at two distinct time periods. Early exacerbation of mass effect (within 48 hours) was related to acute hematoma expansion.[33] Later progression was the result of peri-hematomal cerebral edema, which occurred between 9 and 21 days after the original bleed.[33] This delayed progression of edema and mass effect from days to weeks after ICH provides strong supportive clinical evidence of a secondary injury. Other investigators have also observed that mass effect and cerebral edema persists longer after ICH than ischemic stroke, with mass effect lasting for up to one month in some cases.[34-37]

Studies of regional perfusion in humans have largely failed to demonstrate significant regions of ischemia in the brain surrounding ICH.[38,39] On the contrary, a wealth of pre-clinical evidence has shown that thrombin, hemoglobin, iron and other hemoglobin breakdown products have a significant potential for direct toxic effects upon brain tissue.[40-42]

Theoretically, the early evacuation of blood products could alleviate local mass effect and improve regional perfusion, and, in addition, reduce the volume of blood products and substrate contributing to hemotoxicity, thus reducing or eliminating these potential mechanisms of secondary injury. At the same time, the procedure would be best done in the least invasive manner possible as to avoid inducing additional injury to the brain.

1.3.1 The Case for Minimally Invasive Hematoma Evacuation

The failure of conventional surgical evacuation to improve outcomes in ICH has been attributed to the morbidity associated with the craniotomy and surgical approach. Specifically, it has been proposed that the surgical approach to the hematoma may cause enough damage to surrounding brain to offset any potential benefits of surgery.[42] Correspondingly, it is possible that the potential benefits of hematoma evacuation could be realized if the procedure could be performed through minimally invasive access.

A large meta-analysis of surgical treatment strategies for ICH concluded that surgery could be beneficial in patients undergoing early surgery (within 8 hours), with moderately sized hemorrhages (20 – 50 cc), of moderate age (50 – 69 years)

and with moderate to severe clinical deficits (GCS 9 – 12).[43] Incidentally, an evaluation of the contributing data sets indicates that a single study by Wang et al[44] largely drove the clinical benefit in each of the cohorts.

In the study by Wang et al[44], 465 patients with moderate volume intracranial hemorrhage (ranging between 25 and 40 cc). Patients were randomized to either medical management or minimally invasive craniopuncture therapy. The craniopuncture procedure consisted of the CT-guided placement of a puncture needle into the hematoma. Following the aspiration of hematoma fluid, a lysis fluid (containing urokinase) was injected under pressure into the hematoma. The drainage needle was secured into position and allowed to drain for 3 – 5 days after placement. Using this technique, the authors reported a significant improvement in clinical outcomes with 41% of the craniopuncture group and 63% of the medical management group being dependent (mRS > 2) at 90 days.[44]

Kim et al[45] performed a similar randomized trial in Korea, randomizing 387 patients with small to moderate sized hemorrhages (average volume 23 cc, range 10.4 – 30.0 cc) between MIS and medical management. MIS was performed using an Archimedes screw placed under stereotactic guidance through a burr hole access. They reported significant improvements in clinical outcomes as measured by both Barthel Index (90.9 vs. 62.4, $p < 0.05$) and modified Rankin Scale (1.2 vs. 3.0, $p < 0.05$) at 6 months.[45]

This minimally invasive CT-guided craniopuncture technique is routinely practiced in China with over 150,000 patients undergoing this procedure yearly.[44,46] Zhou et al[46] reported a meta-analysis of 12 studies including 1955 patients randomized between medical management and minimally invasive surgery. These investigators reported robust reductions in both death (46% relative risk reduction) and death or dependence (47% relative risk reduction) at the end of follow-up in subjects undergoing MIS.[46] Additionally, a meta-analysis by Yang et al. corroborates this finding, reporting a significant reduction in mortality or dependence for subjects treated with MIS versus medical management (OR 0.52, 95% CI 0.33 – 0.80, $p = 0.003$). Conversely, craniotomy failed to demonstrate significant clinical outcome compared to conventional management (OR 0.72, 95% CI 0.42 – 1.22, $p = 0.22$).[47]

Recently, two small pilot randomized controlled trials of MIS for ICH have been completed in the United States – The Minimally Invasive Surgery plus tPA for ICH Evacuation (MISTIE) and the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR IVH).[48,49]

In MISTIE, 96 patients were randomized between conventional medical management (n = 42) and minimally invasive surgery (n = 54). The minimally invasive surgical procedure consisted of the initial stereotactic placement of a sheath with manual aspiration of the hematoma followed by the placement of a flexible drainage catheter that was irrigated with tPA for up to four days.[48] These investigators reported a significant reduction in perihematomal edema as well as

trends toward better clinical outcomes at 180 and 365 days.[48,50] They also observed an improvement in mobility and independence in Activities of Daily Living (ADL) at follow-up, as well as a reduction in length of stay and healthcare expenditures. Moreover, the degree of improvement in clinical outcome appeared to be directly related to the volume of hemorrhage remaining at the end of the treatment, with those subjects with < 10 cc's of residual hemorrhage having the best outcomes. Unfortunately, only a minority of subjects in the MISTIE study achieved this level of residual hematoma volume. Moreover, it often took several days of treatment before this level of hematoma reduction was reached.

In the CLEAR IVH trial, patients with small supratentorial hemorrhages and large associated intraventricular hemorrhages requiring ventricular drainage were randomized between saline infusion and intrathecal tPA (IT-tPA) through a ventricular drain.[49] These investigators observed that IT-tPA infusion increased the rate at which the IVH cleared. Moreover, subjects with more rapid and complete clearance of IVH demonstrated a more rapid and complete improvement in neurological status. Although a robust signal for a beneficial effect was observed in the IT-tPA group overall, 6 of 26 subjects (23%) in this cohort experienced symptomatic re-hemorrhage, with three requiring a craniotomy for management. This symptomatic re-hemorrhage rate was considerably higher than that observed for irrigation of parenchymal drainage catheters in MISTIE II. Moreover, it required an average of 10 days to achieve adequate clearance of IVH in the IT-tPA group.

Recently, data regarding the safety and efficacy of intrathecal tPA in the setting of IVH became available for the CLEAR III trial.[51] In this pivotal trial, patients with small or no ICH (≤ 30 cm^3) with associated IVH requiring an EVD were randomized to either placebo (normal saline) or r-tPA (1.0 mg) q8 hours (for ≤ 12 doses) infused through the EVD. The primary outcome measure was mRS ≤ 3 at 180 days. The trial demonstrated that although intraventricular tPA had no effect on clinical outcomes in the entire cohort, there was a significant (11%, $p = 0.006$) reduction in mortality at 180 days. Moreover, safety parameters regarding serious adverse events were more favorable for the tPA cohort (46% vs. 60%, $p = 0.002$). In the subset of subjects with IVH volumes > 20 cm^3, intraventricular-tPA significantly improved rates of good functional outcome (mRS score 0 – 3). More efficient and more complete (> 80%) removal of IVH were directly correlated with patient outcomes. However, most subjects (≈ 70%) did not achieve a substantial (> 80%) reduction in IVH with the CLEAR III tPA infusion technique.[51,52]

Thus, the existing clinical evidence provides support to the pre-clinical data suggesting that the evacuation of blood products after ICH could prevent secondary injury and improve outcomes. However, the current techniques are relatively rudimentary and have several potentially important shortcomings.

First, it requires days to achieve an adequate evacuation of blood products using the craniopuncture and catheter drainage techniques. Optimally, the removal of

blood products should be accomplished as efficiently as is feasible and safe to limit or eliminate the potential for secondary injury related to local hypoperfusion and/or hemotoxicity. Second, the requirement for an indwelling drainage catheter with periodic access for irrigation presents the potential for infection and also is labor and resource intensive. This irrigation is typically performed within an intensive care unit setting. In addition, patients undergoing tPA infusions require multiple serial scans to assess the reduction in hematoma volume and to survey for re-bleeding. Finally, there is some risk of inducing re-bleeding with the infusion of tPA after surgery.

1.3.2 The Case for Minimally Invasive Hematoma Evacuation using a Mechanical Device

Several mechanical techniques have been devised for the minimally invasive evacuation of intracranial hemorrhage. A primarily mechanical approach offers several potential advantages. First, an effective mechanical approach provides a means by which to achieve an immediate, efficient, and predictable reduction in hemorrhage volume. This is particularly true if the technique is performed with direct visualization and/or periodic active monitoring with cross-sectional CT imaging and/or ultrasound. It stands to reason that an immediate and substantial reduction in blood product volume may better reduce the cumulative secondary injury than would a gradual reduction over several days. Second, with some purely mechanical approaches, no post-procedural drainage catheter is required, eliminating the resources required for the maintenance of the catheter as well as the potential for infection or additional hemorrhage associated with catheter manipulation. Third, the avoidance of catheter irrigation with tPA reduces the potential for re-hemorrhage secondary to the local thrombolytic effect.

1.3.2.1 Intra-operative CT-guided Endoscopic Surgery for ICH (ICES)

The ICES technique involves the stereotactic placement of an endoscopic sheath into the hematoma. The hematoma is then evacuated using suction and irrigation from two pre-specified depths. The endoscope is then used to make an assessment of the volume of residual hemorrhage as well as to assess, and potentially control, any active intracranial hemorrhage using cautery.[53] In a small, single-center series of six patients, the operators were able to achieve an 80% reduction in hemorrhage volume and a 60% reduction in midline shift. In a second small, single-center trial, ten patients were randomized between the ICES technique and medical management. In the ICES group (n = 6), the operators achieved an 80% reduction in hematoma volume, while the medical management group demonstrated an 80% enlargement, both over a 24-hour period after treatment allocation.[54] The trial was ultimately halted due to slow enrollment and the recognition from the operators that the technique required optimization within the context of a single-arm study prior to the performance of a randomized trial. Recently, a larger trial by Vespa et al[55] randomized 14 patients to receive ICES and 4 to receive medical management. The control arm of the

MISTIE trial was also used to analyze the trial outcome. Results demonstrated a 71.2% reduction in ICH immediately post treatment; at 72 hours, the reduction in ICH volume was significant (21.1 cm^3, p = 0.0002) in the ICES group as compared to the medical group. Despite being underpowered to yield significant clinical outcome, there was a trend towards good neurological outcome (mRS ≤ 3) for the ICES cohort (42.9% vs. 23.7%, p = 0.19). Notably, the trial demonstrated the feasibility of ICES as a safe and effective modality with a potential to yield good clinical outcome.[55]

The MISTIE II trial evaluated safety and efficacy of hematoma evacuation after ICH using minimally invasive surgery and rt-PA in ICH evacuation in 2 stages (dose finding occurred in 2005-2009 and safety analysis during 2009-2012).[72] There were seventy-nine surgical subjects and 39 medical subjects with minimally invasive surgery and rt-PA in ICH evacuation for mean hematoma volume; 69 subjects in the surgery cohort underwent surgical aspiration and rt-PA and 10 subjects underwent surgical aspiration alone. The reduction in edema was 5.6 in the surgical arm and -11.4 in the medical arm (P<0.001) and the authors concluded that the finding was consistent with the hypothesis that hematoma evacuation would lead to a significant reduction in edema volume.

The MISTIE III Trial was a randomized, blinded endpoint, open label, phase III study that was conducted in the U.S., Canada, Europe, Asia, and Australia (Hanley, 2019)[70]. There were 78 hospitals that enrolled and treated 499 patients with an intracerebral hemorrhage (n=250 MISTIE arm and n=249 standard medical arm). The MISTIE arm subjects were treated with image-guided minimally invasive catheter evacuation followed by thrombolysis.

The main objective was to asses if minimally invasive surgery (MIS) followed by thrombolytic irrigation of the catheterized intracerebral hemorrhagic clot was safe and could improve functional outcomes at 365 days after a stroke. The primary efficacy outcome was good functional outcome (mRs score 0-3) at 365 days after a stroke and the safety outcomes were all-cause mortality at 30 days, procedure related mortality at 7 days, bacterial brain infection at 30 days, and symptomatic bleeding within 72 hours from last dose. The trial used an imaging core lab and a Data Safety Monitoring Board (DSMB) reviewed clinical safety data.

The trial arms were well matched, but there was a higher number of subjects actively taking anticoagulants at the time of enrollment in the MISTIE arm (10%) compared to the SOC arm (4%). For the primary outcome of the mITT set after adjusting for baseline variables, 45% of subjects (n=249) in the MISTIE arm achieved an mRS score of 0-3 at 365 days compared to 41% in the SOC arm (n=240). The MISTIE arm had fewer subjects that

died within 7 days compared to the SOC arm (1% vs 4%, P=0.018, respectively) and also at 30 days (9% vs 15%, P=0.066), respectively. There were 2 bacterial brain infections with 30 days in the MISTIE arm and none in the SOC arm. The MISTIE arm and SOC arm had comparable symptomatic brain bleeds with 72 hours from the last thrombolytic dose (2% vs 1%, P=0.325). However, asymptomatic brain bleeds within 72 hours from the last thrombolytic dose was significantly higher in the MISTIE arm. There were fewer serious adverse events reported in the MISTIE arm compared to the SOC arm (126 events vs 142, P=0.012), which was statistically significant. The authors reported that an exploratory analysis of clot removal did show an association between extent of removal and a lower mRS score (0-3), possibly due to the benefit of the procedure or due to unmeasured confounding effects. Furthermore, the authors concluded that there were few negative consequences to MISTIE, and it was safe with regards to serious bleeding and infection. The procedural risks were also reported as comparable between the two arms.

Another analysis of the MISTIE III data was published (Awad et al.2019) to examine results of a multivariate and univariate model to assess hematoma evacuation efficacy in relation to mRS scores of 0-3.[71] Using a linear spline model, the authors determined that a reduction of ICH hematoma volume of $\leq$15 mL correlated with a good functional outcome of mRS 0-3 (OR 0.90, 95% CI 0.85-0.96, p= 0.002). The results indicated that a reduction beyond the 15 mL threshold increased the chance of having a good outcome by 10% per mL of hematoma removed. The reduction of hematoma volume by $\geq$70% increased the likelihood to achieve an mRS 0-3 score; each additional mL removed beyond 70% translated to a 6% improvement to achieve a good outcome for mRS 0-3 (OR 1.06, 95% CI 1.02-1.10, p=0.002). End of treatment ICH volume < 30 mL also had a significant better survival outcome (OR 5.545, CI 2.362-13.019, p<0.001). At $\leq$ 30 mL end of treatment ICH volume, or >53% volume reduction, a mortality benefit was observed. Initial hematoma volume, history of hypertension, irregular-shaped hematoma, number of alteplase doses given, surgical protocol deviations, and catheter manipulation problems were significant factors in failing to achieve $\leq$15mL goal evacuation. The analysis was significant, as it was the first report of thresholds for reduction of ICH volume correlated with mortality and functional outcomes.

1.4 Conclusions

Intracranial hemorrhage is a devastating disease associated with poor clinical outcomes. To date, no surgical or medical therapy has been demonstrated to improve outcomes in these patients. Of all the strategies tested, the most encouraging data exist for minimally invasive strategies employed to achieve a reduction in hemorrhage volume. Initial data derived from preliminary studies of thrombolytic-assisted catheter drainage have been encouraging, but there are

significant potential shortcomings of this technique compared to the purely mechanical approach with the Artemis Neuro Evacuation Device (Artemis Device). Early experience with the Apollo/Artemis in regards to its application to remove parenchymal hemorrhages has evolved. As such, now that the technical approach has matured, it is necessary to proceed with a pivotal randomized controlled trial to assess the potential for clinical benefit and safety of MIS with the Artemis Device in patients with supratentorial ICH.

2. The Artemis Neuro Evacuation Device

A successor to the Apollo System, the Artemis Device is a surgical instrument designed to aid a physician in the removal of tissue and/or fluid during image-guided neurosurgery. The Artemis Device has two functions. These functions are control and transfer of aspiration and generation of rotational energy. Aspiration is generated by a Penumbra Aspiration Pump, which the Artemis Device connects to through flexible tubing. The Artemis Device has a rigid cannula containing a wire to facilitate removing tissue and/or fluid with the assistance of rotational energy and aspiration. The Artemis cannula fits through the working channels of commercially available neuroendoscopes (e.g. Lotta, Karl Storz, Tuttlington, Germany) such that clot evacuation can be performed under direct visualization.[56] The technique is very similar to the ICES technique in that a sheath is placed within the hematoma and evacuation is typically performed under direct endoscopic visualization. In some settings, periodic evaluation of the remaining hematoma is performed using intra-procedural CT or ultrasound.[56] The method of action of removal is first vacuum aspiration, which draws the tissue and/or fluid into the lumen of the Artemis cannula. Next, the wire inside the lumen of the Artemis cannula is rotated, facilitating movement of any tissue and/or fluid that may otherwise clog the cannula lumen.

The conceptual principles of operation remain the same for the Artemis Neuro Evacuation Device and the Apollo System, both of which are used for the controlled aspiration of tissue and/or fluid removal.

The Artemis Device utilizes rotational energy, rather than vibrational energy used for the Apollo System, to prevent clogging of tissue and/or fluid aspirated into the Artemis cannula. The helical wire prevents the Artemis cannula from clogging by interacting with the aspirated tissue and/or fluid throughout the entire length of the cannula. The electrical power to rotate the wire in the Artemis cannula is provided by a battery which drives a motor, both of which are contained in the disposable handle.

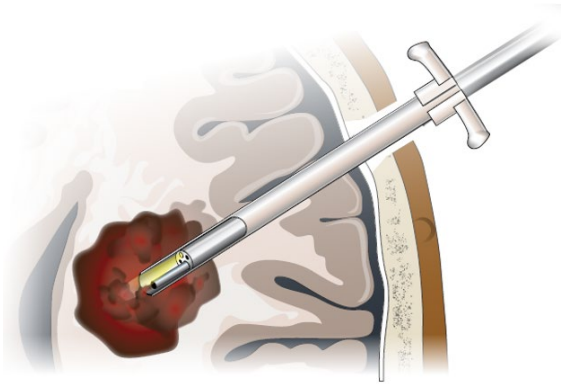
In an initial multi-center, retrospective series of 29 ICH patients undergoing treatment with the Apollo System, an average reduction in hemorrhage volume of 54% was achieved, with a reduction of the hemorrhage volume to < 10 cm^3 in 48% of subjects treated. As opposed to the ICES technique, in most cases, no drainage catheters were placed following the initial evacuation.[56]

Thus, the Artemis Device potentially provides a means by which to efficiently and reliably achieve a minimally invasive, mechanical evacuation of intracranial hemorrhage under

direct visualization and control using a neuroendoscope without the requirement for subsequent catheter placement and thrombolytic irrigation.

The Apollo System received FDA clearance for the controlled aspiration of tissue and/or fluid during surgery of the ventricular system or cerebrum in March 17, 2016 and CE marking in May 10, 2016 and is commercially available in the United States and throughout Europe. The Artemis Neuro Evacuation Device received FDA clearance (K171332) on August 14, 2017.

Figure 1: Image of the Artemis Neuro Evacuation Device cannula at Site of Bleed



3. Risk Analysis

The overall risks associated with the procedure depend on a number of factors including, but not limited to, the device, anesthesia, disease condition and medical management. The primary risks to subjects in this study are associated with the minimally invasive surgical (MIS) procedure and the associated general anesthetic. Imaging performed throughout the course of the study, while specified in the protocol, falls within the standard of care for the initial evaluation and follow-up of patients with intracranial hemorrhage. The MIS procedure is performed in a manner which is similar to that of other neuroendoscopic procedures and the associated risks are similar. In brief (see Section 6.7 for a detailed description of the procedure), the MIS procedure involves the creation of a burr hole/1 – 2 cm craniectomy and dural incision. An endoscopic sheath is then placed through the access site into the hematoma under imaging control using neuronavigation. Under endoscopic guidance, the hemorrhage is evacuated using the Artemis Device. Following the evacuation, the endoscope and Artemis Device are removed. Intraoperative CT imaging is performed to assess the remaining hemorrhage volume and to assess for immediate procedural complications. Ultrasound may also be used during the procedure to evaluate removal of the hematoma. Based on the intra-operative CT imaging, either an additional pass(es) is made or the procedure is terminated. Following the procedure, all equipment is removed and the cranial access is closed in a standard manner.

The potential clinical risks that may be associated with the use of Artemis Device or with the procedure include, but may not be limited to:

Hematoma expansion	Increased blood pressure
Fever	Infections
Headaches	Seizures
Vomiting	Intraventricular hemorrhage
Hyperglycemia	Hydrocephalus
Edema	Thromboembolic events
Re-bleeding	Decreased consciousness
Death	Craniotomy
Bleeding	Unintended Removal of Tissue leading to Neurological and/or sensory deficit

The complications particularly related to the procedure include bleeding, infection, or damage to surrounding structures during the creation of the cranial access or placement of the sheath. During evacuation of the hemorrhage with the Artemis Device, there is the possibility of inducing or encountering an additional hemorrhage in the operative bed. In a retrospective multicenter study of the Apollo procedure for the treatment of ICH, re-bleeding was encountered in 2 of 29 subjects (6.9%).[56] There may be residual fluid or blood requiring additional surgery in the future.

The risk related to the general anesthetic in this patient population is estimated to be approximately 1 – 5% for major morbidity and mortality (e.g. airway management issues, aspiration, hypotension or drug reaction), given that their American Stroke Association score would typically be 4 or 4e in this category of patients.[57,58] A thorough risk analysis was performed as part of design control recommendations of the Quality System Regulation (21 CFR 820).

Best medical management (MM) will be provided as specified in the AHA/ESO guidelines.[18,59] As such, for subjects randomized to the MM arm of the study, there is no additional risk. With the natural history of ICH/IVH and standard of care, there are expected medical events, or expected adverse experiences, that are listed below. Since these medical events are expected in the disease process or after MM, the events are thus expected to occur in any patients with the disease irrespective of the treatment arm. Best medical management (MM) will be provided as specified in the AHA/ESO guidelines.[19,60] As such, for subjects randomized the MM only arm of the study, there is no additional risk.

EXPECTED EVENTS	
Nervous System	Other Systems
Cerebral Edema and Mass Effect	Acute Kidney Injury
Brain Stem Compression	Acute Respiratory Distress Syndrome
Brain Herniation	Aspiration
Brain Re-bleeding near Initial Hemorrhage Site	Catheter-related vascular infections
Catheter Tract Bleeding/Hemorrhage Enlargement	Deep Vein Thrombosis
Cerebral Infarction	Dysphagia
Cerebritis	Fever/Hyperthermia

Coma	Hyponatremia
Death	Hypoxia
Decreased Level of Consciousness	Hypercapnia
Delirium	Hyperglycemia/Hypoglycemia
Diaschisis	Hypertension (Induced or Not Induced)
Elevated ICP	Hypotension (Induced or Not Induced)
Headache	Impaired Nutritional Status
Hydrocephalus	Infectious Complications
Intracranial Abscess	Nausea
Meningitis (Bacterial or Non-Bacterial)	Vomiting
Perihematomal Ischemia	Pericarditis
Seizures	Pulmonary Edema
Ventriculitis (Bacterial or Non-Bacterial)	Pneumonia (including Ventilator-Associated)
	Pulmonary Embolus
	Sepsis/Bacteremia
	Spontaneous Bleeding from Non-Cerebral Sites
	Thromboembolic Complications
	Urinary Tract Infections
	Vascular Injury/Puncture Site Bleeding

Medical Management of ICH should include[18]:

- **Hemostasis and Coagulopathy, Antiplatelet Agents, and Thromboembolic Prophylaxis:** Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism beginning the day of hospital admission.
- **Blood Pressure Management:** Early BP reduction with an SBP target of 140 mmHg for patients with ICH presenting with an SBP between 150 and 220 mmHg and without any contraindication to acute BP treatment. For patients with ICH presenting with an SBP > 220 mmHg, aggressive BP reduction with continuous intravenous infusion and frequent BP monitoring may be reasonable.
- **General Monitoring and Nursing Care:** Initial monitoring and management of patients with ICH should take place in an intensive care unit or dedicated stroke unit with physician and nursing neuroscience acute care expertise.
- **Glucose Management:** Glucose should be monitored. Both hyperglycemia and hypoglycemia should be avoided.
- **Seizures and Antiseizure Drugs:** Clinical seizures should be treated with antiseizure drugs. Patients with a change in mental status who are found to have electrographic seizures on electroencephalography should be treated with antiseizure drugs.
- **Management of Medical Complications:** A formal screening procedure for dysphagia should be performed in all patients before the initiation of oral intake to reduce the risk for pneumonia.

- **Prevention of Recurrent ICH:** BP should be controlled in all patients with ICH. Measures to control BP should begin immediately after ICH onset.
- **Rehabilitation and Recovery:** Given the potentially serious nature and complex pattern of evolving disability and the increasing evidence for efficacy, it is recommended that all patients with ICH have access to multidisciplinary rehabilitation.

In order to minimize risks to subjects enrolled into the clinical study, Investigators will be qualified in accordance with FDA requirements and Good Clinical Practice. Investigators using the devices will be trained on proper use of the Artemis Device in accordance with Section 8.1 herein prior to initiation of treatment at each facility. Patients will be carefully evaluated before treatment to ensure that the treatment with the Artemis Device is appropriate. During treatment, the procedure should be performed in an operating room (OR) or a procedure room with appropriate resources for emergent intervention should complications arise. All treating facilities should conform to national guidelines, and the treating physician should be experienced in treating patients presenting with this condition.

Subjects will be carefully monitored during the procedure and the follow-up period. Clinical study participants will be routinely questioned to confirm whether adverse events/effects have occurred at study visits. The physician should examine and perform various diagnostic tests before, during, and after the procedure with appropriate long-term follow-up.

The anticipated risks will be monitored during the study for changes in event rates. On-going monitoring of adverse events, serious adverse events, and device malfunctions will be conducted during the study. A Clinical Events Committee (CEC) will adjudicate pre-defined AE/SAEs for causality and attribution. A Data Safety Monitoring Board (DSMB) will monitor the overall safety during the clinical study. Penumbra, Inc. or its representatives will continue to monitor the complaints and report them as mandated by FDA or other national agencies.

4. Study Overview

The primary aim of minimally invasive surgery (MIS) for supratentorial intracranial hemorrhage is to achieve an atraumatic evacuation of blood products from the brain to prevent the secondary injury that occurs after the initial bleed. To date, several pilot studies and a small Phase II feasibility trial have suggested that MIS with catheter mediated thrombolytic irrigation may be associated with an improvement in clinical outcomes in ICH.[44,48,50,54,60-62] Currently no prospective study exists to evaluate the efficacy of MIS with the Artemis Device for this purpose. The purpose of this pivotal randomized study is to demonstrate the efficacy of MIS with the Artemis Device to improve outcomes in patients with small to moderate volume supratentorial ICH.

4.1 Study Design

This is a prospective, multicenter randomized study comparing MIS with MM (MIS group) with MM alone in patients with supratentorial intracerebral hemorrhages.

MM will be determined by practice standards utilized in the operator's region of practice and following the existing AHA/ESO guidelines (as above). Patients will be enrolled who meet the inclusion and exclusion criteria, with consent to participate, and are randomized to either MIS or MM. Subjects will be randomly assigned by a central web-based system in a 2:1 manner to treatment with MIS or MM. Data for each subject will be collected at the time of enrollment and treatment, and at subsequent follow-up visits.

4.2 Study Objectives/Endpoints

4.2.1 Primary Endpoints

The primary objective is to demonstrate the efficacy of MIS in patients with supratentorial intracranial hemorrhage to improve clinical outcomes when compared with best medical therapy with respect to the endpoints defined as:

- Efficacy Endpoint: 180 day global disability assessed via the ordinal modified Rankin score (mRS)
- Safety Endpoint: Rate of mortality at 30 days

4.2.2 Secondary Endpoints

- Weighted mRS at 180 days
- mRS of ≤ 3 at 180 days
- mRS of ≤ 2 at 180 days
- mRS at 365 days
- Stroke Impact Scale – Mobility at 180 days
- Stroke Impact Scale – ADLs at 180 days
- Stroke Impact Scale – Mobility at 365 days
- Stroke Impact Scale – ADLs at 365 days
- EQ-5D-5L at 180 days
- EQ-5D-5L at 365 days
- Length of hospital stay
- Length of ICU stay
- Length of procedure

4.3 Method of Randomization

Randomization takes place centrally through a commercially available Interactive Web Response System (IWRS). Randomization will occur in a 2:1 ratio to either MIS or MM. The treatment allocation will be balanced by Hemphill Score (0 – 2, 3 – 4) and hemorrhage location (primarily lobar, primarily deep). Once a patient is determined to meet all study eligibility criteria, the Investigator (or authorized team member) obtains the treatment assignment for that subject. Crossover is not permitted after randomization. Once a subject is randomized, the subject is

considered enrolled in the study and that subject must be followed through to the end of study or to subject's termination of consent.

4.4 Blinding

The protocol is designed to have open label treatment assignment. The Penumbra, Inc. clinical team, the Investigator, site study personnel, and the subject will not be blinded to each subject's randomized treatment group throughout the course of the study. Each site will designate one or more individual(s) to perform the blinded mRS assessment at 180 days. The blinded evaluator(s) will be identified on the Delegation of Authority Log and shall not perform data entry or any other tasks that would reveal the study arm assignment of subjects. Due to the nature of the procedure, subjects will be provided with a hat at the 180 day mRS assessment to prevent the blinded assessor from seeing a scar. If the blind is broken for any reason, this will be documented on the case report forms. The blinded evaluator who performs the mRS assessment will be instructed to follow a scripted interview to control for potential bias.

5. Study Population

5.1 Inclusion Criteria

1. Patient age $\geq$ 18 and $\leq$ 80
2. Supratentorial ICH of volume $\geq$ 20 and $\leq$ 80 cc (measured using A x B x C/2 method)
3. Hemostasis as confirmed by no arterial spot sign (may perform additional scan(s) every 6 hours to demonstrate hemostasis)
4. NIHSS $\geq$ 6
5. GCS $\geq$ 5 and $\leq$ 15
6. Historical mRS 0 or 1
7. Symptom onset < 24 hours prior to initial CT/MR
8. MIS must be initiated within 72 hours of ictus/bleed
9. SBP must be < 180 mmHg and controlled at this level for at least 6 hours

5.2 Exclusion Criteria

1. Imaging
   a. "Arterial Spot Sign" identified on final CTA indicating expanding hemorrhage
   b. Hemorrhagic lesion such as a vascular malformation (cavernous malformation, AVM etc), aneurysm, and/or neoplasm
   c. Hemorrhagic conversion of an underlying ischemic stroke
   d. Infratentorial hemorrhage
   e. Primary thalamic ICH (where the center of the hemorrhage emulates from the thalamus)

f. Associated intra-ventricular hemorrhage requiring treatment for IVH-related mass effect or shift due to trapped ventricle (EVD for ICP management is allowed)
g. Midbrain extension/involvement
h. Absolute contraindication to CTA, conventional angiography, and MRA

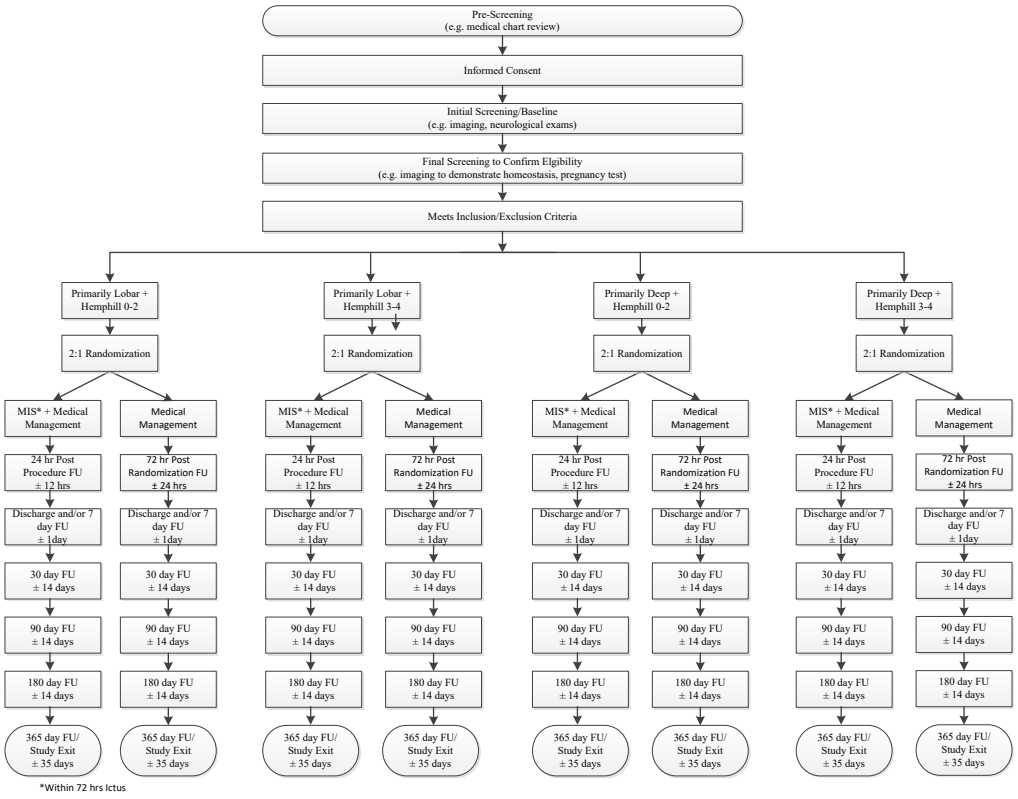
2. Coagulation Issues
   a. Absolute requirement for long-term anti-coagulation (e.g., mechanical valve replacement (bio-prostatic valve is permitted), high risk atrial fibrillation)
   b. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency
   c. Platelet count < 100 x 10^3 cells/mm^3 or known platelet dysfunction
   d. INR > 1.4, elevated prothrombin time or activated partial thromboplastin time (aPTT), which cannot be corrected or otherwise accounted for (i.e., lupus anti-coagulant)
   e. Use of direct factor Xa inhibitors (e.g. apixaban, rivaroxaban, fondaparinux) within last 48 hours
3. Patient Factors
   a. Traumatic ICH
   b. High risk atrial fibrillation (e.g., mitral stenosis with atrial fibrillation) and/or symptomatic carotid stenosis
   c. Requirement for emergent surgical decompression or uncontrolled ICP after EVD
   d. Unable to obtain consent per Institution Review Board/Ethics Committee policy
   e. Pregnancy, or positive pregnancy test (either serum or urine). Women of child-bearing potential must have a negative pregnancy test prior to enrollment
   f. Severe active infection requiring treatment (e.g. sepsis, purulent wound) at the time of enrollment
   g. Renal failure indicated by creatinine > 2 mg/dL or undergoing dialysis
   h. Any comorbid disease or condition expected to compromise survival or ability to complete follow-up assessments through 365 days
   i. Based on Investigator's judgement, patient is unwilling or unable to comply with protocol follow up appointment schedule
   j. Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements
   k. Currently participating in another interventional (drug, device, etc.) clinical trial. Patients in observational, natural history, and/or epidemiological studies not involving intervention are eligible

6. Study Procedures

6.1 Overview of Study Flow

All sites will keep a screen failure log of all ICH patients presenting within 24 hours of symptom onset but who are not randomized into the study. Reason(s) for exclusion will be recorded. Screening information will be reported in an electronic data capture system (EDC). Recruitment rates will be tracked over time for each site. The actual recruitment rates as well as potential recruitment rates will be useful for planning further clinical trials and determining the potential impact of the therapy.

Figure 2: Study Flow



6.2 Study Visits

Subjects enrolled in this study will follow the visit schedule below and will continue to receive standard of care treatment at each follow up visit.

- Initial Screening/Baseline
- Final Screening
- Treatment Procedure (if randomized to MIS)
- Post procedure (within 24 (± 12) hours, MIS subjects) or 72 (± 24, MM) hours after presentation
- 7 days post-enrollment or discharge (whichever comes first)
- Discharge (if beyond 7 days)
- 1 month (defined as 30 days) follow-up (± 14 days)
- 3 month (defined as 90 days) follow-up (± 14 days)

- 6 month (defined as 180 days) follow-up (± 21 days)
- 12 month (defined as 365 days) follow-up (± 35 days)

6.3 Recruitment

The target population are patients ≥ 18 and ≤ 80 years of age who have a diagnosis of spontaneous, non-traumatic, intracerebral hemorrhage (ICH) ranging ≥ 20 and ≤ 80 cc, with an associated significant neurological deficit (NIHSS ≥ 6) who do not require emergent open surgical decompression related to uncontrolled intracranial pressure or mass effect.

Potential study subjects will be identified by the study team at each site to determine eligibility and obtain consent. The study allows for enrollment up to 500 subjects at up to 50 sites globally.

6.4 Screening and Baseline Evaluation

The subject should be clinically evaluated in the same manner as any patient with non-traumatic spontaneous intra-parenchymal hemorrhage which includes medical history screened, available clinical/neurological exams (focused exam, NIHSS, GCS, historical mRS and Barthel Index) obtained, laboratory work, and imaging information per institutional standard of care. Selected concomitant medication and standard of care lab values will be recorded.

Patients will be screened against study eligibility criteria during standard clinical practice. A signed study-specific Institutional Review Board (IRB)/Ethics Committee (EC) approved informed consent form (ICF) must be obtained before performing any test that goes beyond standard clinical care. In any case, consent must be obtained before randomization/enrollment.

The neurologic examinations used to confirm eligibility should be performed by a study team member trained to administer the exams and able to give unbiased neurological and functional assessments (NIHSS, Glasgow Coma Score (GCS), and perform a historical mRS determination). These exams were chosen on the basis of their reliability, familiarity to the neurologic community, adaptability for use in patients who have had a stroke, and comparability to end points used in other trials of intracranial hemorrhage. All scores will be recorded in source documentation and entered into the electronic case report forms (eCRFs). All of the following are found in the Appendix, if permitted per licensing agreements.

- modified Rankin Scale: mRS is an overall assessment of global handicap. mRS must be done by a certified examiner, if not a physician. A historical mRS will be obtained to assess the patient's level of function prior to the ICH.

- Barthel Index: The Barthel Index is an ordinal scale used to measure performance of activities of daily living. A historical Barthel Index score will be obtained to assess the patient's level of function prior to the ICH.

- The National Institutes of Health Stroke Scale: A 42-point scale that quantifies neurologic deficits in 11 categories. Normal function without neurologic deficit is given a score of zero. NIHSS must be done by a certified examiner, if not a physician, as close to the specified times as possible.

- Glasgow Coma Scale: A neurological scale which aims to give a reliable and objective way of recording the conscious state of a person for initial as well as subsequent assessment. A subject is assessed against the criteria of the scale, and the resulting points give a subject score between 3 (indicating deep unconsciousness) and either 15 (fully awake person).

The CT or MR imaging performed to provide a diagnosis of ICH will be used to determine hemorrhage volume using the A x B x C/2 method.

A CTA (or MRA) performed, as standard of care to rule out vascular malformations or aneurysm as well used to determine the presence of "Arterial Spot Sign" to identify an active bleed. If an active bleed is detected, additional CT/CTA/MRAs may be taken every 6 hours if per standard of care at institution and within 72 hours of ictus until hemostasis is confirmed.

An NIHSS and GCS score must be obtained prior to enrollment. The NIHSS score must be ≥ 6 and the GCS score ≥ 5 and ≤ 15 for inclusion in the study.

The Hemphill Score will be assigned based upon the clinical presentation and imaging.

A pregnancy test must be conducted for applicable subjects (female, < 50 years old and of child bearing potential).

If patient meets all eligibility criteria, they will be randomized 2:1 to either MIS or best MM alone. After a subject is randomized they will be considered enrolled. Randomization will be balanced using stratification based upon presenting condition (Hemphill Score) and hemorrhage location (primarily lobar vs. primarily deep). If randomized to surgery, MIS must be performed within 72 hours of the ictus.

6.5 Informed Consent

The Investigator or designee will obtain written informed consent from the subject or approved delegate using the current IRB/EC approved consent form per IRB/EC policy. Consent must be obtained prior to enrollment into the study.

For sites in the United States, informed consent must be obtained by the subject, unless the subject is unable to make the decision to participate in a clinical study (e.g. unconscious subject) in which case a Legally Authorized Representative (LAR) can be utilized.

All informed consent documents used under this protocol will be consistent with applicable elements of EN ISO14155, Clinical investigation of medical devices for human subjects - Good clinical practice and 21 CFR Part 50 and 54, and will be approved by the site's reviewing IRB/EC prior to study initiation.

6.6 Randomization

After all inclusion and exclusion criteria is confirmed and written informed consent obtained, randomization will occur as described above in section 4.3. Randomization is day 0 for determining follow-up visit dates.

6.7 Treatment Procedure

The treatment procedure is described briefly below. The study procedure will take place within 72 hours of the ictus – after completion of the clinical baseline assessment, the presentation and imaging, and following randomization.

6.7.1 Preparation for Treatment

Subjects randomized to the control group will receive best MM for ICH as determined by the stroke physician. All physicians will follow current AHA/ESO guidelines for the treatment of ICH.[18,59] {Hemphill, 2015 #1049;Steiner, 2014 #2487}Subjects randomized to MIS will also receive best MM in addition to the procedure. Reversible coagulopathies at presentation will be corrected as determined by the physician managing the subject. Ventricular drains will be placed as deemed necessary by the managing interventional team to manage ICPs.

MIS will be performed under general anesthesia. The MIS procedure must occur within 72 hours of ictus. The subject should be prepared for the planned intervention according to standard hospital procedures. MIS will be performed as described below (6.7.4)

6.7.2 Medication during Intervention

Medications may be administered during the procedure as determined by the attending anesthesiologist and/or interventionist in accordance with standard of care at each facility. For all subjects, tPA is excluded during the procedure.

6.7.3 Devices and Equipment

In addition to the Artemis Device, other devices needed for the procedure are listed in Table 1. Such devices should be used in accordance with the manufacturer's indication and instructions for use.

Table 1: Devices that may be used during the MIS procedure.

Standard Cranial Access Devices and Endoscopy Sheath	All FDA cleared or CE marked (as applicable) cranial access systems and suitably sized

	endoscopy sheaths (19 F or smaller) will be allowed in the study (e.g., Aesculap Inc, Center Valley, PA).
Neuronavigation System	All FDA cleared or CE marked (as applicable) neuronavigation systems will be allowed in the study Including: • Neuronavigation software, (e.g., iPlan Net, Brainlab, Feldkerchin Germany) • Neuronavigation Localization Mechanism (Skull Reference Base with Skull Reference Array with Reflective Marker Spheres, e.g., Brainlab) • Localization Array (Instrument Adapter Clamp with Instrument Adapter Array, e.g., Brainlab)
Penumbra Aspiration System	The Aspiration Pump and canister for all FDA cleared or CE marked (as applicable) Penumbra Aspiration Systems will be allowed in the study
Neuroendoscopy System or Equivalent	All FDA cleared or CE marked (as applicable) neuroendoscopy systems (e.g., Lotta, Karl Storz, Tuttlington, Germany) which incorporate a working channel that will accommodate either the 1.5, 2.1, or 2.8 mm Artemis Device will be allowed in the study. Exoscope use is not permitted.
CT Monitoring (within or outside of OR)	All FDA cleared or CE marked (as applicable) computed tomography or cone beam computed tomography systems will be allowed in the study (e.g., dynaCT, Siemens, Medical Imaging, Erlangen, Germany).

All medical therapy decisions should be in accordance with guidelines from the AHA/ESO or critical care guidelines.

6.7.4 Procedural Protocol

The Artemis Device and Penumbra Aspiration Pump and canister usage shall follow the Instructions For Use (IFU).

Appropriately protocoled (depending on the institution and neuronavigation units) MR or CT imaging studies will be uploaded into the neuronavigation software for procedural planning and guidance. A trajectory will be selected that is both technically feasible and allows access to the longest possible axis of the hematoma and limits damage to adjacent healthy brain tissue.

Subjects will be placed supine or prone upon the procedural table, and a sterile field prepared. An external localization array or other neuronavigation localization mechanism will be placed for registration. Following registration, a second sterile field will be prepared over the region of the cranial access. A burr hole/1 – 2 cm craniectomy will then be created in a standard manner of a size large enough to accommodate the selected endoscopy sheath. A localization array will be attached to the hub of the selected neuroendoscopic sheath and registered to the navigation system. It is advisable that the neuroendoscope is also registered to the navigation system whenever possible. The sheath will then be advanced using neuronavigation into the targeted landing zone within the distal aspect of the hematoma and once in place the inner obturator removed. The sheath will then be stabilized (e.g., manually stabilized, mechanically stabilized, or peeled away and stapled down) into position. The neuroendoscope will then be inserted into the sheath and under direct visualization the Artemis cannula will be placed through the working channel of the neuroendoscope. The sheath will be irrigated at the discretion of the operator using one of the irrigation ports of the endoscope while keeping the opposite port open at all times to avoid an increase in ICP and the irrigant will be intermittently or continually aspirated until a clear working view is created within the sheath that allows visualization of the surgical field at the sheath tip.

When organized hematoma is visualized at the tip of the sheath, the Artemis cannula will be advanced under direct visualization to, or just beyond the tip of the sheath and actuated to evacuate the blood products. If the working view becomes obscured by blood products within the sheath, additional irrigation and aspiration will be performed to clear the field. When all accessible blood products are cleared from the working field, the sheath will be retracted serially and the procedure repeated. The position of the sheath and/or endoscope will be continually monitored directly using the neuronavigation system. This technique of evacuating the hemorrhage from distal to proximal will be performed until the sheath has been withdrawn through the entire long axis of the hematoma as documented on the neuronavigation. Ultrasound can be used as a tool to visualize the hematoma.

At that point, the neuroendoscopic and Artemis Device will be removed. An intra-operative CT will then be performed using cone-beam CT, an intra-operative or portable conventional CT unit, or the OR room (or procedure room) will be held open for re-operation(s) and the subject may be scanned on a conventional departmental CT unit with the option to immediately return to the OR room, if necessary. The control CT will function to confirm adequate hematoma evacuation and to assess for any complications (e.g., re-bleeding, hydrocephalus, increased mass effect). Additional evacuation will be performed as specified above at the discretion of the operator, based upon the data from the CT. It is recommended to achieve a 65% reduction in hemorrhage volume and a final hemorrhage volume of < 15cc.[50]

After the hemorrhage evacuation is completed, the sheath will be removed and the cranial access site will be closed in a standard manner.

6.7.5 Post-Procedure Care

Subjects randomized to both groups will receive MM for ICH as determined by the attending physician. Standardization of medical management in both arms will occur according to the following:

- General medical management according to AHA/ESO guidelines[18,59]
- Admission to monitored or intensive care unit for at least 24 hours
- Close monitoring of BP with treatment according to AHA/ESO guidelines[18,59]
- Follow-up imaging studies as indicated in any patient with neurologic deterioration

Additional imaging will be obtained at the discretion of the managing service based upon clinical data and established institutional standard of care. Images may need to be sent into the Sponsor and/or Core Lab for further review.

The subject will be recovered from the procedure (if randomized to MIS) and discharged from the hospital as per standard practices.

6.8 24 hours post MIS or 72 hours post randomization (MM subjects)

MIS Group:

- A post-procedural CT scan will be obtained within 24 hours (± 12 hours) in all subjects undergoing MIS.
- Neurological and functional exams will be conducted within 24 hours (± 12 hours) in subjects undergoing MIS, assessment completed according to Table 2.

MM Group:

- A CT (preferred) or MR will also be obtained in MM subjects 72 hours (± 24 hours) after randomization.
- Neurological and functional exams will be conducted within 72 hours (± 24 hours) of randomization in subjects undergoing MM, assessment completed according to Table 2.

The volume of hemorrhage on the diagnostic scan will be calculated using a standard A x B x C/2 calculation. On the CT slice with the largest area of ICH, the largest diameter (A) is measured in cm. The dimension of the hemorrhage perpendicular to the largest diameter (B), represents the second diameter. The third diameter (C) will be calculated either by multiplying the number of CT slices which depict the hematoma by the slide thickness or determined on coronal or sagittal reconstructions.

6.9 Day 7/Discharge

The subject may be discharged from the hospital when clinically stable, at the Investigator's discretion. At day 7, the following will be completed by a qualified member of the research or clinical care team: a focused physical exam, a neurological exam (including GCS, NIHSS and mRS), a review of any adverse events, and a review of selected current medications. If discharge occurs before 7 days after randomization, the discharge clinical examinations will also substitute for the 7-day clinical evaluation and a standard of care CT (preferred) or MR will be obtained at that time. For subjects who remain in the hospital past Day 7, only SAEs and neurological AEs are reportable. For all subjects who expire prior to the Day 7/Discharge assessment, available information regarding the primary cause of death will be recorded, as well as whether the subject made "do not resuscitate" (DNR) prior to expiration.

6.10 Post Discharge Follow-Up

The designated staff at the clinical site will review the study requirements with the subject to maximize compliance with the follow-up schedule. The staff will instruct subjects to return for follow-up assessments according to the Schedule of Assessments in Table 2. Study staff should establish a date and time for the follow-up visits with the subject, if possible, at the time of hospital discharge.

The study will be considered complete after all subjects have completed 365 day (± 35 days) follow-up assessment as outlined in Table 2. Requirements of each follow-up evaluation are detailed below. Post Discharge, all subjects will be followed-up after 30 days (± 14 days), 90 days (± 14 days), 180 days (± 21 days), and 365 days (± 35 days). The 90 day visit can be done via a clinical visit or a telephone call.

6.10.1 Post Discharge Assessments

- Focused Exam, which includes a review of subject's vitals.
- mRS: As described in section 6.4 above. It is preferred that mRS measurements are done at the study site, but if subject is unable to come into the study site for the follow-up visit, a mRS evaluation may be obtained via telephone for 30 day, 90 day, and 365 day using the approved telephone questionnaire/worksheet. The 180 day evaluation of mRS must be conducted in-person.
- Barthel Index: As described in section 6.4 above.
- NIHSS: As described in section 6.4 above.
- GCS: As described in section 6.4 above.

- EQ-5D-5L is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, the questionnaire provides a simple descriptive profile and a single index value for health status. The 90 day EQ-5D-5L should be done using the approved telephone questionnaire if the visit is conducted via the telephone.

- Stroke Impact Scale: Additionally, a quality of life scale outcome measure will be utilized in this study. Quality of life scales are designed to be sensitive to changes in outcome from mild and moderate stroke undetected by other outcome measures. Important parameters not fully interrogated by conventional outcome scales can be assessed by quality of life scales, including emotion, communication, cognition, and social role function. Standard measures, such as the mRS, primarily evaluate physical aspects of stroke outcome, not addressing more relevant quality of life measures. The Stroke Impact Scale is a validated assessment of quality of life specifically in patients with stroke.[63]

All day 30, day 90, day 180, and day 365 outcome measures will be assessed by a qualified member of the research or clinical team. The schedule of neurological assessments is listed in Table 2. At each visit, the subject medical record will be surveyed for any new or interim neurological adverse or serious adverse events and selected concomitant medication. In addition, the subject, LAR, or approved delegate will be asked about any interim neurological adverse or serious adverse events. The subject, LAR, or approved delegate will also be specifically asked about any interim neurosurgical procedures. Best medical management should be followed throughout the post discharge follow up period.

6.10.2 Unscheduled Visits

If a subject returns to the study site between follow-up visits a focused exam and mRS value should be obtained and recorded in the unscheduled visit CRF. Subject should also be screened for reportable adverse events and any medications used to treat those events, as well as any changes to medications should be recorded.

Table 2: Schedule of Assessments*

ACTIVITY	INITIAL SCREENING / BASELINE	FINAL SCREENING	TREATMENT PROCEDURE	*MM ONLY:* 72-HOUR POST RAND (±24 hours)	*MIS ONLY:* 24- HOUR POST ARTEMIS (±12 hours)	DISCHARGE AND /OR 7 DAYS (± 1 day)	30 DAY (± 14 days)	90 DAY PHONE CALL (± 14 days)	180 DAY (± 21 days)	365 DAY (± 35 days)	UN SCHEDULED
Informed Consent	X										
Verify I/E Criteria	X										
Medical History	X										
Focused Exam	X			X	X	X	X		X	X	X
Standard of Care Labs	X	X[2]		X	X	X					
Pregnancy Test[4]	X										
CT/MR	X[1]	X[1,2,3]	X	X[1]	X[1]	X[2]					
CTA or MRA	X	X[3]									
Barthel Index	Historic						X	X	X	X	
NIHSS	X[2]	X[6]		X[6]	X[6]	X[6]	X[6]	X[2, 6]	X[6]	X[6]	X[2]
GCS	X[2]	X		X	X	X	X	X[2]	X	X	X[2]
mRS[6]	Historic			X	X	X	X	X	X[8]	X	X
Randomization		X[7]									
Artemis Procedure[5]			X								
Stroke Impact Scale (QoL)							X		X	X	
EQ-5D-5L QoL							X	X	X	X	
Con Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Review			X	X	X	X	X	X	X	X	X

[1] Image to be sent to central core lab within 14 days of 72-hr post randomization (MM group) or 24-hr post Artemis (MIS group) visit
[2] If done as standard of care
[3] As necessary to demonstrate hemostasis
[4] For Women of childbearing potential
[5] Under general anesthesia within 72 hours of ictus if randomized to MIS group
[6] Performed by certified assessor (or physician) delegated for task
[7] After all eligibility criteria confirmed
[8] Performed by blinded certified assessor (or physician) delegated for task
[*] Subjects in both MM and MIS group should follow medical management per AHA/ESO guidelines

7. Investigator Responsibilities

7.1 Institutional Review Board/Ethics Committee Approval

Prior to enrolling patients into the study, the investigator will ensure that proper IRB/EC approval is obtained in accordance with applicable local state and federal laws and regulations. The IRB/EC shall approve all study documents as appropriate, including but not limited to the final protocol, amendments to the protocol, Instructions for Use, and the Informed Consent Form.

The investigator will report to the Sponsor or designee immediately if, for any reason, the approval to conduct the investigation is withdrawn by the IRB/EC or Competent Authority. The report will include a complete description of the reason(s) for which approval was withdrawn.

7.2 Informed Consent

The investigator is responsible for ensuring that a signed and dated informed consent is obtained in accordance with Section 6.5 of this protocol and according to country and local requirements prior to conducting any study-related assessments, prior to administration of any pre-procedure medications or sedation, and prior to enrolment into the study.

7.3 Adherence to Protocol/Amendments and Applicable Law

The investigator is responsible for overseeing, ensuring that the study is conducted, and completing the study according to this protocol and in accordance with the relevant aspects of EN ISO 14155:2011, Declaration of Helsinki, along with any conditions imposed by the reviewing IRB or EC and all other applicable regulations. The investigator shall approve and adhere to this protocol and any amendments that arise during the course of the study.

It is the investigator's responsibility to ensure that the staff assisting with the study have the appropriate qualifications, are fully instructed on the study procedures, and will respect the confidentiality statement.

7.4 Case Report Form Completion

The investigator and study staff shall complete the case report forms (CRFs) associated with this study. Subject numbers shall be used to identify individual subjects in this study. The CRFs should be a complete and accurate record of subject data collected during the study according to relevant aspects of ISO 14155 and Good Clinical Practices (GCP) requirements. It is the investigator's responsibility to ensure the quality of the data collected and recorded.

7.5 Image Upload

Sites will be provided with instructions for how images should be collected and submitted within 14 days of the acquisition of the final required imaging at 72-hr post randomization (MM group) or 24-hr post Artemis (MIS group) visit. Additional images may be requested for adverse event adjudication. In the case of rebleeding immediate post procedure image may be requested for upload. If the site is unable to provide the images within this timeframe, the appropriate Sponsor contact should be notified. Study staff shall ensure that no images contain protected health information or personally identifying information as defined per local regulatory requirements.

7.6 Reporting

The investigator will be responsible for reporting the following:

7.6.1 Adverse Events

Adverse events or adverse device effects must be recorded by the investigator on the CRFs and must be carefully monitored during the study. All adverse events will be collected starting at enrollment through discharge and/or 7 day visit. After discharge and/or 7 day visit, all SAEs and neurological AEs are reportable through final follow-up visit.

Minimum requirements of data to be recorded are: type of event, duration of event (start through end), seriousness, action taken, outcome, and causality.

In order to ensure prompt reporting of AEs, we require that all reportable AEs (as well as all related study data) be entered timely into the Electronic Data Capturing (EDC) web-based database. All UADE should be reported immediately by calling Penumbra Clinical Affairs and all SAEs should be reported in the EDC within 72 hours of the study site staff first being made aware of the occurrence of the SAE. If the EDC system is unavailable, a written report can be sent via email to Penumbra.

The investigator must report the SAE or ADE to the IRB/EC according to local requirements. Reporting time frames should comply with local or national requirements. In addition, the investigator should report to the Sponsor and IRB/EC any device malfunctions that could have led to a SAE, if required by national regulations or by local authorities.

For the purpose of reporting within this protocol, pre-existing conditions or planned procedures for pre-existing conditions are not reported as AEs unless there is worsening of the condition with an increase in severity or frequency during the course of the investigation. An event does not need to be reported as a SAE if it represents a relapse or an expected change or progression of the condition. This type of event is considered an AE. All deaths should be reported regardless of causality. When reporting a death, the primary condition or

diagnosis that contributed to the fatal outcome should be reported as a SAE with an outcome of death. If the cause of death is unknown, please report "unknown cause of death" as an SAE.

Detailed form and narrative reports of the following specific adverse events will be obtained:

- Death (all cause) within 30 days of enrollment
- Death within 7 days of enrollment: Immediate periprocedural death
- Symptomatic Re-Hemorrhage or New Hemorrhagic Event: Any new intracranial hemorrhage or increase in size of pre-existing hemorrhage (IPH, IVH or extra-axial bleed) within 30 days associated with an NIHSS increase of ≥ 4 or a GCS decrease > 2 persisting for at least 24 hours, requiring emergency surgical decompression or resulting in death.
- Symptomatic Evolution of Perihematomal Edema: Edema with increased mass effect or uncontrolled ICPs within 30 days requiring emergency surgical decompression NOT related to new or increased hemorrhage (i.e. edema related) associated with an NIHSS increase of ≥ 4 or a GCS decrease > 2 persisting for at least 24 hours, requiring emergency surgical decompression or resulting in death.
- Symptomatic Ischemic Stroke: A new ischemic stroke (ipsilateral, contralateral; contiguous with bleed/operative site or remote; cortical, subcortical or perforator distribution) within 30 days associated with an NIHSS increase of ≥ 4 or a GCS decrease > 2 persisting for at least 24 hours, requiring emergency surgical decompression or resulting in death.
- Surgical complications related to MIS: Surgical site infection, brain abscess or confirmed meningitis, or documented complication(s) deemed specifically related to the procedural anesthetic (medication, access or intubation related) within 30 days.

7.6.1.1 Analysis of Adverse Events

A medical monitor will review these specific categories of events as they are reported. The medical monitor has the authority to alert the DSMB at any time if a potential safety issue arises. If at any point, these reviews raise any safety concerns, the DSMB will be empowered to suggest that the study be placed on hold and request additional analyses of the study dataset. At the end of each DSMB meeting, the board shall recommend study (i) continuance according to protocol, (ii) modification of the protocol, or (iii) early study termination. The DSMB shall base their recommendations on all available evidence and their collective expertise and judgement. Safety stopping rules for the primary safety endpoint will be developed and used to help the DSMB make its safety assessments. Additional details regarding the DSMB structure, frequency of meetings and stopping rules will be included in the DSMB charter.

In addition to the reporting requirements noted above, pre-defined AE/SAEs will be evaluated by the Clinical Events Committee (CEC) for an independent analysis at regularly scheduled meetings according to the CEC Charter. Redacted source documents will be collected for events requiring adjudication and for other events where the medical monitor deems necessary.

7.6.1.2 Definitions

- **Adverse Event (AE)**: An AE is any undesirable clinical event occurring to a patient, during a clinical trial, whether or not it is considered related to the device. This includes a change in a patient's condition or laboratory results which has or could have a deleterious effect on the patient's health or well-being.

- **Adverse Device Effect (ADE):** An adverse event related to study device(s).

- **Serious Adverse Event (SAE):** A SAE is an event that:

    - Led to death
    - Led to a serious deterioration in the health of the patient that:
        - Resulted in life-threatening illness or injury
        - Resulted in permanent impairment of a body structure or a body function
        - Required in-patient hospitalization or prolongation of existing hospitalization
        - Resulted in medical or surgical intervention to arrest permanent impairment to body structure or a body function
        - Led to Chronic Disease
        - Led to fetal distress, fetal death or a congenital abnormality or birth defect

- **Unanticipated Adverse Device Effect (UADE):** Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not identified in nature, severity or degree of incidence in the protocol or IFU or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.6.1.3 Event Relationship

The investigator will categorize the relation of the adverse event as follows:

- **Index ICH:** Event is clearly attributable to underlying disease state with no temporal relationship to the device or treatment

- **Index Procedure:** Event has a strong temporal relationship to the procedure with no relationship to the Artemis Device but may have relationship to ancillary devices used to perform the procedure. Adverse events occurring more than 7 days after the MIS procedure are not expected to be considered related to the procedure

- **Artemis Neuro Evacuation Device:** Event has a strong temporal relationship to the device and alternative etiology is less likely

    - The Artemis Device consists of: powered handle, cannula, tubing and suction connector

7.6.1.4 Relationship to Study Device

An AE is considered to be device-related when it is reasonable to believe that the event may have been caused by or is related to the device. The following definitions will be used to assess the relationship of the adverse event to the use of study device. Any grading for relatedness other than 'unrelated' will be considered device related.

- **Definite:** The temporal sequence is relevant and the event abates upon device application completion/removal, or reappearance of the event on repeat device application.

- **Probable:** The temporal sequence is relevant or the AE abates upon device application completion/removal or the AE cannot be reasonably explained by the subject's condition or comorbidities. The AE is related or most likely associated with the device.

- **Possible:** The temporal sequence between the device and the AE is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the subject's condition. There is a possibility of a relationship between the AE and the device.

- **Unrelated:** The AE is not associated with the device. There is no relation between the AE and the device.

Similar grading will be used for assessing the relationship to index procedure, index ICH, and comorbidities.

7.6.2 Protocol Deviation

Any deviations from the protocol identified during monitoring or through other means should be clearly documented. These include but are not limited to:

- Subject does not meet inclusion/exclusion criteria
- Incomplete or missing data

- Failure to obtain signed informed consent
- Improperly signed or incomplete informed consent
- Delayed reporting of serious adverse events or UADEs
- Out of window visits or assessments

7.6.3 Device Deficiencies

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of the study medical device shall be documented and reported throughout the standard commercial process. Investigators must report all possible device malfunctions or near incidents associated with the device, observed during the course of the study. This includes unexpected outcomes or device malfunctions that might have led to a serious adverse event if (a) suitable action had not been taken or (b) intervention had not been made or (c) if circumstances had been less fortunate.

Device manufacturers are required to report qualifying medical device incidents to the relevant national competent authorities. An incident is defined as "any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject or to a serious deterioration in their state of health". A deterioration in state of health is considered unanticipated if the condition leading to the event was not considered in a risk analysis.

Investigators participating in this study will report all events that could qualify for a vigilance incident to the Sponsor via the commercial process, who will evaluate the incident against the reporting requirements.

7.7 Administration of Neurological Exams and Stroke Scales

The Principal Investigator at each investigative site is responsible for the administration of the neurological examinations and grading of subjects on the stroke scales (i.e., NIHSS, mRS). In cases where a designee is assigned, the investigator must ensure that the designee is trained and has the appropriate qualifications to perform these functions. Assessors of mRS and NIHSS must be certified or practicing physicians.

7.8 Device Disposition

The investigator shall maintain records pertaining to device disposition. The disposition of each device includes:

- Subject number
- Device lot number(s)

The Principal Investigator will ensure that, for the purpose of this investigation, only trained physicians who are sub-investigators in this study will use the Artemis Device on subjects enrolled.

7.9 Records Retention

The investigator shall maintain the records associated with this study for a period of at least two years after either the date on which the investigation is completed or the date that the records are no longer required for supporting a premarket approval/notification submission, whichever is later. Veeva (eTMF) will be used as the master repository for all site and Sponsor regulatory documents with the exception of DICOMs. Sites do not need to maintain a duplicate file unless otherwise mandated by local institution requirements. These records include, but are not limited to the following:

- Correspondence with the Sponsor or designee, core laboratory, and other investigators
- Subject source records, including but not limited to, ICF, copies of all completed CRFs, and supporting documents (laboratory reports and reports of diagnostic tests, medical records, etc.)
- All versions of study protocol with dates and details of reasons for any deviations from the protocol that could affect the scientific quality of the study or the rights, safety, or welfare of the subjects
- Instructions for Use
- Reports of any serious adverse event or serious device effects
- A copy of all approvals related to the clinical investigation
- The approved, blank, informed consent forms and blank CRFs
- All approval/acknowledgment letters from the by the IRB/EC for all versions of the study protocol, ICF and other documents
- Clinical Trial Agreement
- Signed and dated curriculum vitae for all study personnel
- Medical licenses for the Principal Investigator and all participating sub-investigators
- Financial disclosure for the Principal Investigator and all participating sub-investigators
- All required regulatory documents such as Delegation of Authority and training logs
- Signed Protocol Signature Page(s)

8. Sponsor Responsibilities

8.1 Training

The Sponsor is responsible for providing training on the protocol, study device, CRF completion, image upload, and randomization as applicable for all study staff per the Delegation of Authority.

Prior to an Investigator being activated in the study, he/she must complete a minimum of 3 qualified cases to be considered a study operator of the Artemis Device.* Cases must be reviewed by an independent physician(s) prior to Investigator being authorized as a study operator.

- If the Investigator has not used the device in > 3 months, training may be repeated.

*An Investigator may be given a waiver for the outlined training if he/she has been a regular user of the Apollo System and/or Artemis Device.

8.2 Investigator List

The Sponsor shall keep a list of the names, addresses, and professional positions of the clinical investigators for the study.

8.3 Adverse Event Reporting

The Sponsor shall evaluate adverse event reports received from the investigational sites and found during data monitoring and shall report them to the appropriate regulatory bodies and other investigational sites as necessary.

8.4 Data Monitoring

Penumbra is responsible for ensuring that the study is conducted according to the appropriate regulations (US Food and Drug Administration 21 CFR §812, ISO 14155). A Penumbra employee or designee will conduct the following site visits:

8.4.1 Site Qualification Visit

Conducted to ensure the investigational site has the appropriate staff, facilities, and expertise to participate in the study.

8.4.2 Site Initiation Visit

Conducted to train the investigational staff on use of the device, study requirements, and other relevant training.

8.4.3 Interim Monitoring Visit

Conducted as needed to ensure the investigational site is operating in compliance with this protocol, continues to have the appropriate staff and facilities, and is correctly completing the CRFs.

To ensure that investigators and their staff understand and accept their defined responsibilities, the Sponsor will maintain regular correspondence and perform periodic site visits during the course of the study to verify the continued acceptability of the facilities, compliance with the investigational plan, and

maintenance of complete records. Clinical monitoring will include review and resolution of missing or inconsistent data and source document checks to ensure the accuracy of the reported data. Informed consent, CRFs and medical records for all enrolled and screen failed subjects will be made available to the Sponsor for review and collection as agreed with the investigator. The Sponsor will evaluate and summarize the results of each site visit in written reports, identifying repeated data problems with any investigator and specifying recommendations for resolution of noted deficiencies.

8.4.4 Study Close-Out Site Visit

Conducted at the termination of the study or site closure to resolve any outstanding data queries, ensure all regulatory documents are present, and to ensure that any remaining study materials are returned to the Sponsor or properly discarded.

8.5 Data Management

Electronic Case Report Forms (eCRFs) will be used at all investigational sites. All study data will be entered into a commercially available web-based electronic data capture (EDC) system. Data entry will be performed by the study site personnel. Investigators are responsible for completion and timely submission of the data to the Sponsor. Every reasonable effort should be made to complete data entry within 7 days of data collection. This EDC system requires no on-site software installation or specific hardware to operate. Investigators, clinical coordinators, data managers, and Penumbra clinical personnel access project information and study data centrally via a web browser.

Automated data quality checks will display warnings for invalid data. Additionally, manual review of data listings may be used to identify data discrepancies or inconsistencies. The study site may be queried for clarification concerning eCRF discrepancies or inconsistencies identified. If eCRF corrections are necessary, they will be made by the Investigator or an authorized member of the Investigator's staff that is delegated to CRF/EDC. Questions or problems with submitted data will be addressed with the Principal Investigator via an electronic querying system, or through direct contact. The Investigator will review the eCRFs for completeness and accuracy and provide his/her electronic signature and date to eCRFs as evidence thereof. Any data items that have been changed will require reapplication of the electronic signature.

Study personnel will have individual login and password to access the clinical study information based upon each individual’s roles and responsibilities. The application provides hierarchical user permission data entry, viewing, and reporting options. All data entry and data update information, including the date and person performing the action, will be available via the audit trail, which is part of the EDC system.

All eCRFs and other data files will be secured to ensure confidentiality. Investigators are required to maintain source documents required by the protocol, including laboratory results, patient reports, supporting medical records, and informed consent forms. The source documents will be used during the regular monitoring visits to verify information entered on the eCRFs.

For each enrolled subject, required CT/MRs will be appropriately de-identified, and sent to the imaging core lab for evaluation. The core lab and CEC reviews will also be entered into an electronic system. Each reviewer will provide his/her electronic signature and date to reviews as evidence thereof. Queries may be issued in the system or via email to the core lab or CEC for clarification concerning possible EDC discrepancies or inconsistencies.

9. Ethical Considerations

9.1 Declaration of Helsinki

The study will be performed in accordance with the applicable aspects of ISO 14155, recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland (1964 and later revisions), ICH and US FDA GCP guidelines.

It is the responsibility of the investigator to obtain approval of the study protocol from the IRB/EC and to keep the IRB/EC informed of any serious adverse event, serious adverse device effects, and amendments to the protocol. All correspondence with the IRB/EC should be filed by the investigator and copies sent to the Sponsor or its designee.

9.2 Informed Consent

It is the responsibility of the investigator or his/her designee to give each patient full and adequate verbal and written information regarding the objective and procedure of the study and the possible risks involved and to obtain signed informed consent from all patients prior to inclusion in the study unless the patient's health condition does not allow informed consent, in which case the local hospital, state, country, and regulatory procedures will be applied. The original, signed consent is filed with the patient study records, and a copy is provided to the patient.

9.3 Subject Data Protection

Each subject will be assigned a unique subject identification number at the time of enrollment. This subject identification number will be retained throughout the study. Study sites will keep a log that notes the subject’s name and corresponding subject identification number. All case report forms (CRFs) will be tracked, evaluated, and stored using only the subject ID number. No personally identifying information will be included on the case report forms.

The informed consent form will notify subjects that study monitors, auditors, and representatives of government agencies will have access to personally identifying information to ensure that data reported on the CRFs corresponds to the person who signed the consent form and the information contained in the source documentation. The patient must be informed that the data will be stored and analyzed by computer, that national regulations for handling of computerized data will be followed. Furthermore, the patients should be informed about the possibility of inspection of relevant parts of the hospital records by the Sponsor or other Health Authorities including the FDA.

10. Statistical Procedures

The primary objective of this multicenter, randomized, clinical study is to investigate the potential efficacy of MIS to improve clinical outcomes in patients with spontaneous, non-traumatic, ICH presenting within 24 hours in comparison to best MM. The primary hypothesis to be tested is that treatment with MIS will improve outcomes at 180 days as compared to the best MM group. Each eligible subject will be randomized in a 2:1 ratio to either the MIS or best MM with a balanced randomization based upon the hemorrhage location (primarily lobar, primarily deep) and Hemphill Score (0 – 2, 3 – 4). The hemorrhage location and Hemphill Score have been shown to be associated with functional outcome.[6,10,19,25] An adaptive design approach will be utilized to allow for interim analyses and decisions on early stopping for either predicted success or failure.

10.1 Sample Size Estimation for the Primary Outcome

The proposed study is a randomized controlled study designed to demonstrate the efficacy of MIS to improve clinical outcomes across the entire population of patients with supratentorial ICH, as well as to evaluate effect sizes within major anatomical sub-groups (e.g., deep vs. lobar hemorrhage) and cohorts (e.g. age, presenting GCS). In addition, the treatment arm will provide, for the first time, a prospective, independently adjudicated, characterization of the technical outcomes and complication rates associated with the Artemis MIS procedure.

This design provides 81% power for a cumulative odds ratio of 1.7 for the Day 180 mRS. The design's overall one-sided Type I error rate is 2.5%.

The maximum study sample size is 500 subjects and the minimum sample size is 200 subjects. The final study sample size is estimated to be low if the treatment effect is small and the study could be stopped for futility or if the treatment effect is large and the study could be stopped for expected success. The final study sample size will be high if the evidence for the treatment effect is inconclusive.

The Day 180 mRS distribution used for sample size estimation was based on control arm data from the following published studies: MISTIE[48], STICH[13], and SICHPA[64]. The distribution of mRS functional outcomes utilized in the sample size estimation is provided in Table 3.

Table 3. Distribution of mRS Functional Outcomes

mRS Distribution	0	1	2	3	4	5/6
MM	3%	10%	7%	7%	14%	59%
MIS	5%	15%	10%	9%	16%	46%

10.2 Control of Systematic Error and Bias

Randomization takes place centrally through a commercially available Interactive Web Response System (IWRS). The clinical study will be conducted under a common protocol for each investigational site with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each investigational site.

The interim analysis of the primary endpoint will be conducted by an independent statistician.

10.3 Missing Data and Imputation Methods

Every effort will be made to keep all missing data, particularly the Day 180 outcomes, to a minimum. Despite the clinical sites' best efforts, some missing data may be inevitable mainly due to lost-to-follow-up (LTFU). Subjects not completing the 180 day follow-up mRS will be imputed for the primary endpoint using the mRS as of the last available follow-up visit (i.e., Day 30, Day 90) by estimating the probability distribution of the Day 180 mRS conditional on Day 30 or Day 90 mRS. The imputed mRS scores will be utilized in both the interim and final primary analyses. Sensitivity analysis will be performed.

10.4 Definition of Populations

10.4.1 Screened

All patients considered for participation in the study, whether or not they sign an informed consent.

10.4.2 Screen Failure

All patients considered for participation in the study, who failed to meet inclusion criteria or met exclusion criteria. Patients can be screen failed based on general or imaging criteria. These patients may or may not have signed an informed consent.

10.4.3 Enrolled (Randomized)

All subjects who have been randomized based on the result of the baseline imaging and other inclusion/exclusion criteria. Informed consent must be obtained prior to randomization.

10.4.4 Completed

All subjects who were enrolled (randomized) and completed the study follow-up or were known to have died prior to the follow-up timepoint. The completed subject metric will be provided for Day 180 and Day 365 follow-up.

10.4.5 Early Termination:

Subjects who were enrolled (randomized) but did not complete follow-up and were not known to have died. The early termination subject metric will be provided for Day 180 and Day 365 follow-up.

10.5 Definition of Analysis Populations

10.5.1 Target Population

The target population is patients 18 – 80 years of age who have a diagnosis of spontaneous, non-traumatic, intracerebral hemorrhage (ICH) ranging in volume between and including 20 and 80 cc, with an associated significant neurological deficit (NIHSS > 6) who do not require emergent open surgical decompression related to uncontrolled intracranial pressure or mass effect.

10.5.2 Intent to Treat Sample

As the primary analysis, all efficacy and safety outcome measures will be analyzed under the intent-to-treat (ITT) principle. Under this principle, the evaluable sample includes all subjects who are randomized. Each subject will be analyzed according to the treatment group to which they were randomly assigned at the time of randomization. This population is the primary population for all efficacy parameters.

10.5.3 Per Protocol Sample

In addition to the defined ITT analysis sample, a per-protocol (PP) sample is defined as a subset of the ITT sample. The per-protocol sample will include all randomized subjects that do not have significant protocol deviations (e.g., eligibility violation, crossover).

10.5.4 Safety Analysis (As Treated) Sample:

In the case of cross-overs, a safety sample that is the same as the ITT sample will be examined in which subjects will be analyzed according to the actual treatment received. Subjects who receive Artemis device-based therapy are included in the MIS arm and subjects who receive only medical therapy are included in the MM arm.

10.6 Interim Analysis

Interim data analysis of the primary efficacy and safety endpoints is planned after 200 subjects have been enrolled. Additional interim analyses will be conduct after every 50 subjects are enrolled. The interim analyses will include imputing the 180 day mRS score for subjects who do not have a 180 day score. Based on the predictive probability that the study would be a success the study may be stopped early for futility or enrollment may be stopped based on expected success. The specific details of the planned analyses are described completely in the adaptive design report.

10.7 Statistical Evaluation of Primary Endpoint

The primary endpoint is the Day 180 global disability assessed via the ordinal modified Rankin score (mRS).

The null hypothesis is that the cumulative odds ratio for mRS at 180 days in the MIS group compared to MM group is less than or equal to 1. The alternative hypothesis is that the cumulative odds ratio for mRS at 180 days is greater than 1. Formally, the null and alternative hypotheses to be tested are as follows:

H_0: OR ≤ 1

H_A: OR > 1,

where OR is the cumulative odds ratio for the mRS at the 180 day follow-up visit, with higher values indicating better outcomes in the MIS treatment group.

Statistical analysis of the primary endpoint will be conducted using a logistic regression analysis of the 180 day mRS scores. The primary efficacy endpoint is met if the overall treatment effect is positive at a one-sided alpha of 0.02. The odds ratio and corresponding 95% confidence interval will be estimated from the proportional odds model. The primary analysis will be unadjusted. A secondary analysis model will include the minimization variables of Hemphill Score and hemorrhage location.

The mRS scores of 5 and 6 will be combined into a single group for the purposes of endpoint evaluation. Subjects deceased during study follow-up will be scored as mRS 6.

10.8 Statistical Analysis of Primary Safety Outcome

With the date of randomization set at day 0, any death occurring on or before Day 30 will be included as a death.

10.9 Secondary Statistical Analysis

The secondary endpoints of Day 180 and Day 365 average improvement in global disability will be assessed via the weighted modified Rankin score (mRS) and will be analyzed using a generalized linear model. The mRS scores will be weighted as

the following: 1.0 for mRS level 0; 0.91 for mRS level 1; 0.76 for mRS level 2; 0.65 for mRS level 3; 0.33 for mRS level 4; 0 for mRS level 5; and 0 for mRS level 6.[65] Statistical analysis of the dichotomized Rankin outcome scores of 0 to 2 and 0 to 3 will be conducted with a logistic regression model. Group differences will be analyzed for the following: SIS-ADL, SIS-mobility, EQ-5D-5L, length of stay, length of procedure. Other pre-specified analyses will be performed as outlined in the statistical plan.

10.10 Baseline Characteristics

Baseline data will be analyzed to assess the comparability of treatment groups. Baseline data including, but not limited to demographics, clinical characteristics, and baseline ICH characteristics will be summarized using descriptive statistics. Statistical testing will be performed as appropriate.

10.11 Pooling Across Centers

Analyses will be presented by treatment group using data pooled across sites. The site analysis will be conducted using an ordinal logistic regression with terms of treatment group and treatment-by-site interaction. This analysis will be performed on the intent-to-treat population. The primary statistical inference is the treatment-by-site interaction, which is tested at the significance level of 0.15. When the treatment-by-site interaction is statistically significant ($p \leq 0.15$), the treatment group differences will be evaluated within each site. Adjusted analysis on the primary outcome using key baseline variables will be used for the site analyses for consistency with the overall study result. If the odds ratio of the treatment effect is found to vary by site, then a random-effects model analysis will be performed to assess whether there was significant variance in the primary endpoint according to study site.

10.12 Health Economics Information

The study site will complete CRFs containing healthcare utilization information (e.g., ICU days). This information may be used for analyses to compare overall healthcare costs and resource utilization between MIS and MM.

10.13 Final Report

A final report will be completed, even if the study is prematurely terminated. At the conclusion of the study, a multi-center abstract reporting the results will be prepared and may be presented at a major meeting(s). A multi-center publication may also be prepared for publication in a reputable scientific journal. The publication of results from any single center experience within the study is not allowed until the aggregate study results have been published, unless there is written consent from the Sponsor.

11. Study Committees and Core Labs

11.1 Steering Committee/Scientific Advisory Board

The Steering Committee (SC) and/or Scientific Advisory Board (SAB) will be comprised of physicians with subject matter expertise. The SC/SAB will be advisors to the Sponsor regarding study planning, execution and data presentation, progress of enrollment, subject safety and consideration of new information. Daily study management is the responsibility of the Penumbra. The SC/SAB will oversee dissemination of study results through appropriate scientific sessions and publications. The SC/SAB may recommend additional investigators, based on enrollment and adherence to the protocol, to participate on a Publication Committee. The Publication Committee will participate in the review and approval of all requests for data analysis, abstract and manuscript preparation and submission.

11.2 Safety Monitoring Committees

11.2.1 Data Safety Monitoring Board (DSMB)

A DSMB will be comprised of members not participating in the study and will include neurovascular specialist physicians and a statistician. The DSMB will exercise review of the overall safety of the study and make recommendations to adjustments in the study protocol, should any be considered necessary for safety or other related reasons. Additional details will be specified in the DSMB charter.

11.2.2 Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) is made up of independent medical doctors who are not participants in the study. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study which are based on the protocol.

At the onset of the study, the CEC will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. While the CEC review of adverse events specific to the interventional procedure will unblind the members, all members of the CEC will be blinded to the overall primary results of the study.

The CEC will review and adjudicate appropriate clinical events, mainly related to the device and to the study endpoints. The CEC will also review and rule on all deaths that occur throughout the study. The safety process flow and a web-based electronic database will be provided to CEC members for case review and adjudication. The designated Penumbra staff who are responsible for reviewing safety data on an ongoing basis will coordinate collection of information for the event dossier.

11.3 Imaging Core Lab

The independent imaging core lab will review images from the procedure to determine, at a minimum, hematoma volume. An Imaging core lab charter will provide procedure for core lab review. Penumbra, or designee, is responsible for tracking images received, basic quality review and forwarding applicable results to the CEC.

12.Study Administration

12.1 Clinical Trial Termination/Withdrawal

Subjects may be terminated or withdrawn from the study for the following reasons:

- Voluntary withdrawal of consent — Meaning that a subject voluntarily chooses not to participate further in the study. All data collected up to the date of withdrawal of consent will be maintained in the study database. Withdrawn subjects will not have any additional follow-up and will not be replaced.
- Lost to follow-up — A subject will not be considered lost-to-follow-up until contact is not achieved at the 365 day visit. At a minimum, the effort to obtain follow-up information will include three attempts to make contact via telephone or e-mail and if unsuccessful, a letter from the Investigator sent via courier or other traceable method will be sent to the subject's last known address. These efforts to obtain follow-up will be recorded in the subject's study files and the case report forms.
- Subjects may also be withdrawn at the investigator's discretion if within their best interest. A subject's participation in the clinical study will be terminated if the investigator believes that this is in the subject's best medical interest or if the subject no longer complies with the clinical study requirements.

The Sponsor may temporarily suspend or prematurely terminate the study at any time for the following reasons:

- Suspicion of risk to subjects
- If no positive IRB/EC decision is obtained or if the judgement of the IRB/EC is revoked
- If the applicable regulatory body has made an irrevocable objection
- If it transpires that continuation of study cannot serve any scientific purpose, and this is confirmed by the IRB/EC
- Business reasons (e.g., Sponsor has been declared insolvent, or if a petition has been filed for liquidation)

The Sponsor will document reasons for study suspension or premature termination and notify the PIs. The Sponsor will ensure that the IRB/ECs and regulatory authorities (if required) are notified in a timely manner.

The Sponsor will continue to provide resources to fulfill the obligations from the study protocol and existing agreements for following up the subjects enrolled in the study.

The Principal Investigators will promptly inform the enrolled subjects at his/her site, if appropriate.

If the Sponsor temporarily suspends the study and wishes to resume it, the Sponsor will inform the PIs, IRB/ECs and (if appropriate) regulatory authorities. The Sponsor will provide a rationale for resuming the study. IRB/ECs must provide written approval before the study is resumed.

12.2 Stopping the Trial Based on Interim Safety Data

The DSMB will receive periodic safety reports of all reported AEs and SAEs. In addition, the following specific endpoints will be assessed by the medical monitor and presented:

- Death (all cause) within 30 days of enrollment
- Death within 7 days of enrollment: Immediate periprocedural death
- Symptomatic Re-Hemorrhage or New Hemorrhagic Event: Any new intracranial hemorrhage or increase in size of pre-existing hemorrhage (IPH, IVH or extra-axial bleed) within 30 days associated with an increase of 4 or more points on the NIHSS or GCS decrease > 2 persisting for at least 24 hours, requiring emergency surgical decompression or resulting in death
- Symptomatic Evolution of Perihematomal Edema: Edema with increased mass effect or uncontrolled ICPs within 30 days requiring emergency surgical decompression NOT related to new or increased hemorrhage (i.e., edema related) associated with an increase of 4 or more points on the NIHSS or GCS decrease > 2 persisting for at least 24 hours, requiring emergency surgical decompression or resulting in death
- Symptomatic Ischemic Stroke: A new ischemic stroke (ipsilateral, contralateral; contiguous with bleed/operative site or remote; cortical, subcortical or perforator distribution) within 30 days associated with an increase of 4 or more points on the NIHSS or GCS decrease > 2 persisting for at least 24 hours, requiring emergency surgical decompression or resulting in death
- Surgical complications related to MIS: Surgical site infection, brain abscess or confirmed meningitis, or documented complication(s) deemed specifically related to the procedural anesthetic (medication, access or intubation related) within 30 days

Additional details regarding the DSMB structure and stopping rules will be included in the DSMB charter.

12.3 Missing Visits

Any study subject who does not attend a scheduled follow-up visit should be contacted by site personnel to determine the reason for the missed appointment(s).

If the missed visit was due to a serious adverse event, (e.g., re-hospitalization) an AE CRF must be completed and any reporting requirements met. Every effort should be made in order to bring subject in to scheduled follow-up visits.

12.4 Protocol Adherence and Amendments

Prior to beginning the study, the Principal Investigator must sign the protocol signature page documenting his/her agreement to conduct the study in accordance with this protocol. An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Each deviation from the protocol must be documented with the date and reported to Penumbra as soon as possible, and to the IRB/EC per local guidelines and government regulations.

The protocol must be followed exactly. It can be altered only by written amendments made by Penumbra. Following appropriate approval by Penumbra the amended protocol will be submitted to the required regulatory agencies before being distributed to all participating sites. Each site must obtain IRB/EC approval before implementing the revised protocol.

12.5 Trial Registration

The study will be registered in a publicly accessible trial database (e.g., clinicaltrials.gov) prior to study initiation.

13. Publication of Information

All information and data shared by Sponsor and generated by Investigator or Sponsor or other study site in association with this study will be held in strict confidence by the Investigator and shall remain the sole property of Sponsor. Such information may include all information recorded in the EDC or any unpublished study data. All information not previously published concerning the test device and research, including patent applications, manufacturing processes, basic scientific data, etc., is considered confidential and should remain the sole property of Penumbra. The Investigator agrees to use this information for the sole purpose of completing this study and for no other purpose without written consent from the Sponsor.

The results of this study may be offered for publication. The investigators and the Sponsor shall collaborate in the writing of the study to ensure accuracy.

14. Contact Information

The address of Penumbra, Inc. is:

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One Penumbra Place
Alameda, CA 94502
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16. Appendix

16.1 Abbreviations

ADE	Adverse Device Effect
ADL	Activities of Daily Living
AE	Adverse Event
AHA	American Heart Association
aPTT	Activated Partial Thromboplastin Time
ASA	American Society of Anesthesiologists
AVM	Arteriovenous Malformations
BP	Blood Pressure
CE Marking	European Conformity Marking
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CRF	Case Report Form
CT	Computed Tomography
CTA	Computed Tomography Angiography
DNR	Do Not Resuscitate
DSMB	Data Safety Monitoring Board
DVT	Deep Vein Thrombosis
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	Electroencephalogram
ESO	European Stroke Organization
EU	European Union
EVD	External Ventricular Drain
FDA	US Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practices
GCS	Glasgow Coma Score
I/E	Inclusion/Exclusion
ICES	Intra-operative CT-guided endoscopic surgery
ICF	Informed Consent Form
ICH	Intracerebral Hemorrhage

ICP	Intracranial Pressure
ICU	Intensive Care Unit
INR	International Normalized Ratio
IPH	Intraparenchymal Hemorrhage
IRB	Institution Review Board
ISO	International Organization for Standardization
ITT	Intent to Treat
IT-tPA	Intrathecal Tissue Plasminogen Activator
IVH	Intraventricular Hemorrhage
IWRS	Interactive Web Response System
LAR	Legally Authorized Representative
LTFU	Lost to follow-up
MIS	Minimally Invasive Surgery
MM	Medical Management
MR	Magnetic Resonance
MRA	Magnetic Resonance Angiography
mRS	modified Rankin Scale/Score
NIHSS	National Institute of Health Stroke Scale
OR	Operating Room
PHE	Peri-Hematomal Edema
PI	Primary Investigator
PP	Per Protocol
QOL	Quality of Life
rFVIIa	recombinant factor VIIa
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SC	Steering Committee
SIS	Stroke Impact Scale
tPA	Tissue Plasminogen Activator
UADE	Unanticipated Adverse Device Effect

16.2 Modified Rankin Scale[66]

0	No Symptoms at all
1	No significant disability, despite symptoms; able to perform all usual duties and activities
2	Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability; requires some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden; incontinent, and requires constant nursing care and attention
6	Death

16.3 National Institute of Health Stroke Scale[67]

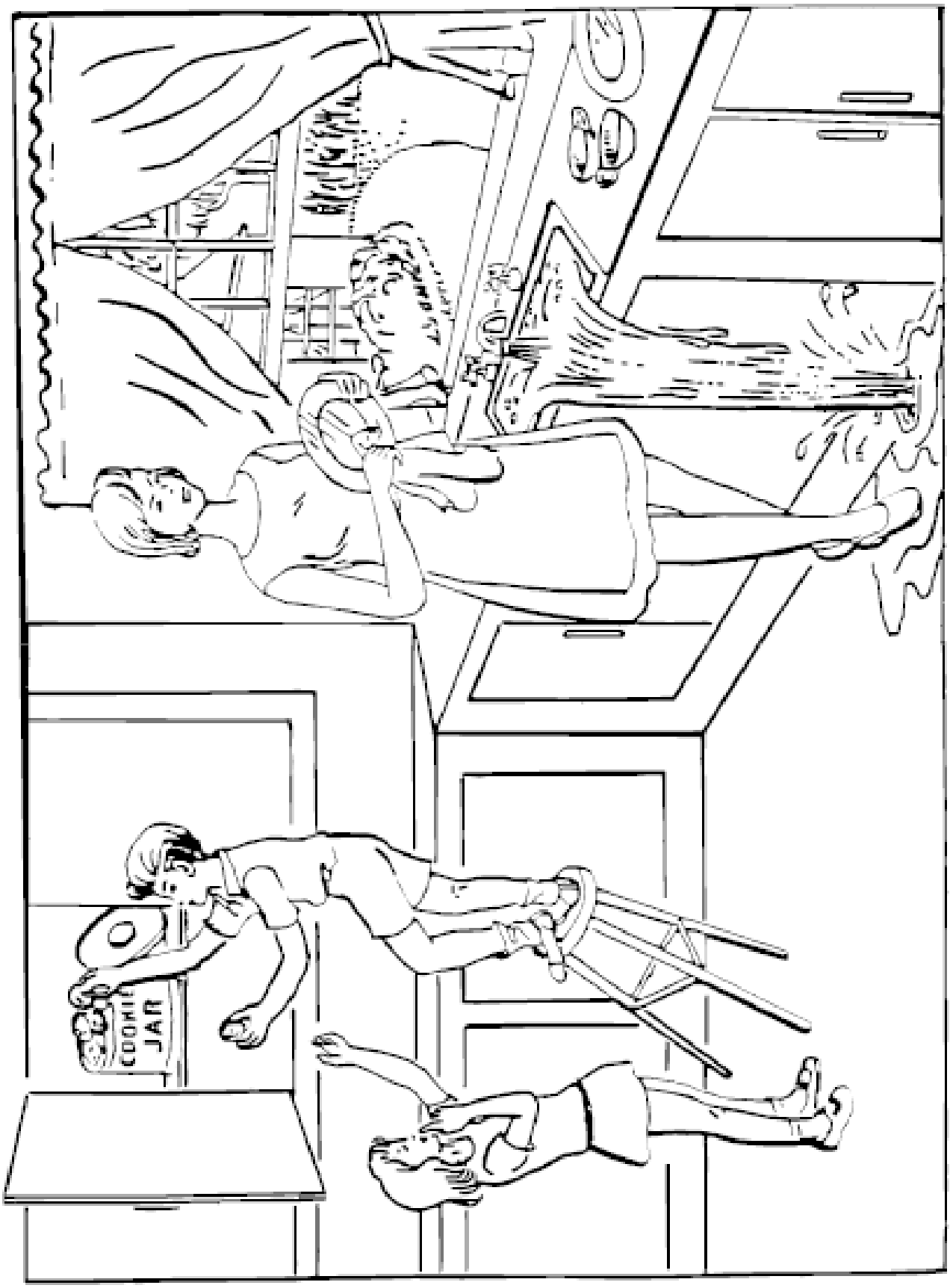
NIH STROKE SCALE		
Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert: keenly responsive. 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor autonomic effects or totally unresponsive, flaccid, and flexic.	___
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct – there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.	___
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him/her (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.	___
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric	0 = Normal.	___

NIH STROKE SCALE		
Instructions	Scale Definition	Score
testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.	
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to answer item 11.	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).	___
4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.	0 = Normal symmetrical movement. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).	___

NIH STROKE SCALE		
Instructions	Scale Definition	Score
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; Limb holds 90 (or 45) degrees, but drifts down before full 10 seconds: does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 5a. Left Arm 5b. Right Arm	 ___
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = No drift; leg holds 30 degrees position for full 5 seconds 1 = Drift; leg falls by the end of the 5 second period but does not hit bed 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity 3 = No effort against gravity; leg falls to bed immediately 4 = No movement UN = Amputation or joint fusion, explain: _____ 6a. Left Leg 6b. Right Leg	 ___
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "UN" and the examiner must clearly write the explanation for not scoring. In case of blindness test by touching nose from extended arm position.	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion, explain: _____	 ___
8. Sensory: Sensation or grimace to pin prick when tested, or withdrawal	0 = Normal; no sensory loss.	 ___

NIH STROKE SCALE		
Instructions	Scale Definition	Score
from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic score 2. Patients in coma (item 1a=3) are automatically given a 2 on this item.	1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.	
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = No aphasia, normal. 1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.	___
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of	0 = Normal. 1 = Mild to moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty.	___

NIH STROKE SCALE		
Instructions	Scale Definition	Score
spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech, may the item be scored as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why (s)he is being tested.	2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier, explain: _____	
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.	___


COOKIE
JAR

You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

16.4 Barthel Index[68]

Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	_____
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	_____
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	_____
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	_____
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____

TOTAL (0–100): _____

16.5 Glasgow Coma Scale[69]

Glasgow Coma Score		
Eye Opening (E)	Verbal Response (V)	Motor Response (M)
4= Open before stimulus (Rating=Spontaneous) 3= After spoken or shouted request (Rating=To sound) 2= After fingertip stimulus (Rating=To pressure) 1= No opening at any time, no interfering factor (Rating=None)	5= Correctly gives name, place and date (Rating=Orientated) 4= Not oriented but communicates coherently (Rating=Confused) 3= Intelligible single words (Rating=Words) 2= Only moans/groan (Rating=Sounds) 1= No audible response, no interfering factor (Rating=None)	6= Obey 2-part request (Rating=Obeys commands) 5= Brings hand above clavicle to stimulus on head/neck (Rating=Localizing) 4= Bends arm at elbow rapidly but features not predominantly abnormal (Rating=Normal flexion) 3= Bends arm at elbow, features clearly predominantly abnormal (Rating=Abnormal flexion) 2= Extends arm at elbow (Rating=Extension) 1= No movement in arms/legs, no interfering factor (Rating=None)
		Total= E+V+M

16.6 Stroke Impact Scale[63]

These questions are about the physical problems which may have occurred as a result of your stroke.

1. In the past week, how would you rate the strength of your....	A lot of strength	Quite a bit of strength	Some strength	A little strength	No strength at all
a. Arm that was most affected by your stroke?	5	4	3	2	1
b. Grip of your hand that was most affected by your stroke?	5	4	3	2	1
c. Leg that was most affected by your stroke?	5	4	3	2	1
d. Foot/ankle that was most affected by your stroke?	5	4	3	2	1

These questions are about your memory and thinking.

2. In the past week, how difficult was it for you to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Extremely difficult
a. Remember things that people just told you?	5	4	3	2	1
b. Remember things that happened the day before?	5	4	3	2	1
c. Remember to do things (e.g. keep scheduled appointments or take medication)?	5	4	3	2	1
d. Remember the day of the week?	5	4	3	2	1
e. Concentrate?	5	4	3	2	1
f. Think quickly?	5	4	3	2	1
g. Solve everyday problems?	5	4	3	2	1

These questions are about how you feel, about changes in your mood and about your ability to control your emotions since your stroke.

3. In the past week, how often did you...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Feel sad?	5	4	3	2	1
b. Feel that there is nobody you are close to?	5	4	3	2	1
c. Feel that you are a burden to others?	5	4	3	2	1
d. Feel that you have nothing to look forward to?	5	4	3	2	1
e. Blame yourself for mistakes that you made?	5	4	3	2	1
f. Enjoy things as much as ever?	5	4	3	2	1
g. Feel quite nervous?	5	4	3	2	1
h. Feel that life is worth living?	5	4	3	2	1
i. Smile and laugh at least once a day?	5	4	3	2	1

The following questions are about your ability to communicate with other people, as well as your ability to understand what you read and what you hear in a conversation.

4. In the past week, how difficult was it to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Extremely difficult
a. Say the name of someone who was in front of you?	5	4	3	2	1
b. Understand what was being said to you in a conversation?	5	4	3	2	1
c. Reply to questions?	5	4	3	2	1
d. Correctly name objects?	5	4	3	2	1
e. Participate in a conversation with a group of people?	5	4	3	2	1
f. Have a conversation on the telephone?	5	4	3	2	1
g. Call another person on the telephone, including selecting the correct phone number and dialing?	5	4	3	2	1

The following questions ask about activities you might do during a typical day.

5. In the past 2 weeks, how difficult was it to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a. Cut your food with a knife and fork?	5	4	3	2	1
b. Dress the top part of your body?	5	4	3	2	1
c. Bathe yourself?	5	4	3	2	1
d. Clip your toenails?	5	4	3	2	1
e. Get to the toilet on time?	5	4	3	2	1
f. Control your bladder (not have an accident)?	5	4	3	2	1
g. Control your bowels (not have an accident)?	5	4	3	2	1
h. Do light household tasks/chores (e.g. dust, make a bed, take out garbage, do the dishes)?	5	4	3	2	1
i. Go shopping?	5	4	3	2	1
j. Do heavy household chores (e.g. vacuum, laundry or yard work)?	5	4	3	2	1

The following questions are about your ability to be mobile, at home and in the community.

6. In the past 2 weeks, how difficult was it to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a. Stay sitting without losing your balance?	5	4	3	2	1
b. Stay standing without losing your balance?	5	4	3	2	1
c. Walk without losing your balance?	5	4	3	2	1
d. Move from a bed to a chair?	5	4	3	2	1
e. Walk one block?	5	4	3	2	1

f. Walk fast?	5	4	3	2	1
g. Climb one flight of stairs?	5	4	3	2	1
h. Climb several flights of stairs?	5	4	3	2	1
i. Get in and out of a car?	5	4	3	2	1

The following questions are about your ability to use your hand that was MOST AFFECTED by your stroke.

7. In the past 2 weeks, how difficult was it to use your hand that was most affected by your stroke to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a. Carry heavy objects (e.g. bag of groceries)?	5	4	3	2	1
b. Turn a doorknob?	5	4	3	2	1
c. Open a can or jar?	5	4	3	2	1
d. Tie a shoe lace?	5	4	3	2	1
e. Pick up a dime?	5	4	3	2	1

The following questions are about how stroke has affected your ability to participate in the activities that you usually do, things that are meaningful to you and help you to find purpose in life.

8. During the past 4 weeks, how much of the time have you been limited in...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Your work (paid, voluntary or other)	5	4	3	2	1
b. Your social activities?	5	4	3	2	1
c. Quiet recreation (crafts, reading)?	5	4	3	2	1
d. Active recreation (sports, outings, travel)?	5	4	3	2	1
e. Your role as a family member and/or friend?	5	4	3	2	1
f. Your participation in spiritual or religious activities?	5	4	3	2	1
g. Your ability to control your life as you wish?	5	4	3	2	1
h. Your ability to help others?	5	4	3	2	1

Stroke Recovery

On a scale of 0 to 100, with 100 representing full recovery and 0 representing no recovery, how much have you recovered from your stroke?

Full Recovery										No Recovery
100	90	80	70	60	50	40	30	20	10	0